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Postgraduate
Medicine

SPECIAL ISSUE

Pediatrics

SEPTEMBER 1957

Care of the Premature Infant

JOSEPH DANCIS*

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JOSEPH DANCIS

PREMATURE birth is the leading cause of death in the neonatal period (figure 1). The mortality rate is highest among premature infants with the lowest birth weights (table 1), and the greatest threat to life occurs during the first week (table 2).

A significant difference between the physiology of the newborn infant and that of the adult is that the latter is capable of maintaining his "internal environment" in the face of extreme stress. The body temperature is kept within narrow limits despite extremes in environmental temperature; the kidneys maintain the concentration of the chemical constituents of the blood at fairly constant levels, and the invasion of pathogens is resisted by a series of body defenses. These functions, which may be grouped loosely as those concerned with homeostasis, are gradually developed during intra-uterine life. By the end of the normal gestation period, they are sufficiently developed to enable most infants to survive under the conditions of modern care. The more prematurely an infant is born, the less developed are these functions and the more precarious is his existence. The temperature, the concentration of the chemical constituents of the blood, the leukocyte count and the respiratory rate vary rather widely in the absence of disease, and symptoms, which are usually evidence of resistance to stress, are often lacking in spite of the presence of serious illness. It is important to keep this in mind in approaching the care of a premature infant.

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Routine Care

When a premature birth appears imminent, it is advisable to have the delivery made in a hospital with a well-equipped and well-staffed premature unit. Obstetric anesthesia and analgesia should be kept minimal in order to pre-

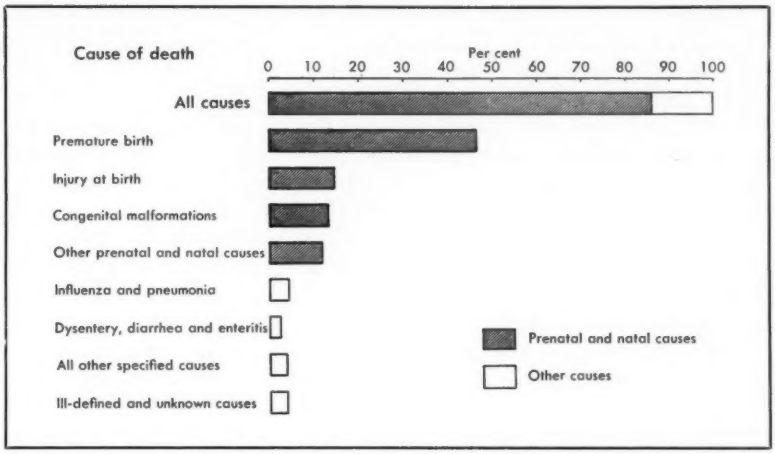

FIGURE 1. Deaths in the first month of life, by cause, in the United States, 1944.

(Dunham, E. C.: Premature Infants. Washington, D.C., United States Government Printing Office, 1948.)

TABLE 1

MORTALITY RATE FOR PREMATURE INFANTS ACCORDING TO BIRTH WEIGHT (MASSACHUSETTS, 1951)*

WEIGHT, GM.	MORTALITY RATE, PER CENT
1000 or less	93.8
1001 to 1500	57.8
1501 to 2000	18.4
2001 to 2500	4.7

*Rice, R. G., Bloom, E., Getting, V, A. and Saunders, S.: Care of the premature infant in Massachusetts. New England J. Med. 248:1090 (June 25) 1953.

TABLE 2

MORTALITY RATE FOR PREMATURE INFANTS ACCORDING TO AGE (UNITED STATES, 1948)*

AGE	MORTALITY RATE, PER CENT
Under 1 day	57.0
1 day to under 1 week	33.2
1 week to under 1 month	7.8
1 month to under 1 year	2.0

*Dunham, E. C.: Premature Infants. Ed. 2. New York, Paul B. Hoeber, Inc., 1955.

vent embarrassment of the respiratory center of the infant, which already may be inefficient. On delivery, the nose and throat of the infant are sucked free of mucus and other fluid, and the stomach is aspirated. One or 2 mg. of vitamin K is administered subcutaneously. The infant is placed in a warm bassinet or a portable incubator,* and transferred to the premature unit.

Control of temperature and humidity—When the infant arrives in the unit, his temperature is taken rectally. This also will determine whether the rectum is patent. If the temperature is low, or if the infant weighs less than 1500 gm. he is placed in an incubator which previously has been warmed to 90° F. The temperature is taken every half-hour at first, and the temperature of the incubator is adjusted according to the temperature of the infant. If the infant is small and his temperature is low, an attempt is made to stabilize the temperature at about 96° to 97° F. Experience has shown that efforts to raise the temperature to the reputed normal of 98.6° F. often result in overheating and an erratic temperature curve. The temperature of the incubator and that of the infant usually are stabilized within two or three hours. After this, the temperatures are checked every three hours as long as the infant remains in the incubator. As he matures, his temperature gradually approaches 98° or 99° F. despite progressive lowering of the temperature of the

*The Premature Transport Service in New York City uses a portable incubator obtained from Pragel Portable Incubators, Inc., Baltimore, Maryland.

incubator. When no external heat is needed, the infant is removed from the incubator.

Silverman[1] recently reported that the mortality rate for a group of premature infants less than five days old who were kept in incubators in which the humidity ranged from 80 to 90 per cent was lower than the mortality rate for a similar group of premature infants who were kept in incubators in which the humidity ranged from 30 to 60 per cent. Both groups were maintained under environmental temperatures of 83° to 85° F. A humidity of 80 to 90 per cent can be obtained only in incubators with forced ventilation (e.g., the ISOLETTE®). But, similar results probably can be accomplished in other incubators by introducing nebulized water. Compressed air is used for nebulization unless oxygen therapy is indicated. There is no evidence that detergents (e.g., ALEVAIRE®) are of any value.

Oxygen therapy—The recent incrimination of the excessive use of oxygen as a cause of retrolental fibroplasia has resulted in a drastic revision in the use of oxygen. Since the introduction of the following regimen, we have not observed any instance of retrolental fibroplasia at the Bellevue Hospital.

1. Oxygen is administered only for the relief of respiratory distress, primarily when cyanosis is present.

TABLE 3

OUTLINE OF FEEDING ROUTINE

PERIOD AFTER BIRTH	FEEDING ROUTINE
24 to 48 hours	Starvation period
Next 12 hours	Determine infant's tolerance for clear fluids; then start milk feedings
5 days	Reach minimal fluid requirement of 110 cc. per kilogram of body weight
7 to 10 days	Reach daily requirement of 120 calories per kilogram
1 week	Start administration of vitamin supplements
3 months	Start administration of ferrous sulfate in daily doses of 50 mg. of elementary iron

2. The oxygen content of the incubator is not permitted to exceed 40 per cent.

3. The need for oxygen is regularly evaluated by briefly discontinuing its administration every eight hours. Its administration is discontinued permanently as soon as possible.

To make certain that the oxygen content of the incubator does not exceed 40 per cent, we use tanks containing a mixture of 40 per cent oxygen and 60 per cent nitrogen. Accurate gauges are available for maintaining low rates of flow of oxygen.* It must be stressed that the only way to know the oxygen content of an incubator is to determine it. Oxygen analyzers are relatively inexpensive, and are very easy to operate. Every premature unit should be equipped with one.†

Feeding—The principles of feeding are rather simple, but the application of these principles is an art. The experience of nurses who specialize in the care of premature infants is an essential ingredient. We are constantly evaluating the child's nutritional requirement on the one hand and balancing it against the dangers of vomiting and aspiration of food on the other. Since the advent of the polyvinyl catheter,‡ the hazards of fatigue and excessive manipulation have been greatly reduced.

There is inadequate knowledge of the requirement for fluids and calories during the first days of life. The general feeling has been that the needs are small, and that more harm has been done by attempting to proceed too fast than too slow. The schedule that we follow is outlined in table 3. A wide variety of milks are used in different medical centers. These include breast milk, breast milk fortified with protein, proprietary milk preparations in which the amount of fat is reduced (ALACTA®) or similar preparations in which the butterfat is replaced with unsaturated

*A flow gauge that we have found satisfactory is one that is manufactured by the Melchior, Armstrong, Dessau Co., Ridgefield, New Jersey.

†A widely used oxygen analyzer is one made by Arnold O. Beckman, Inc., South Pasadena, California.

‡Polyvinyl catheters are made by several firms. The one that we have preferred is made by the Pharmaseal Laboratories, Inc., Glendale, California.

fat (OLAC®). Extensive experience with proprietary infant foods has demonstrated that premature infants can be raised satisfactorily without breast milk, and the great convenience of these foods has led to their widespread use. Balance studies also have given some support for the use of these foods. At the Bellevue Hospital, we use Olac because premature infants absorb unsaturated fats more efficiently than they do saturated fats. However, the good results reported from other clinics in which different milk preparations are used indicate that, within limits, the final outcome is influenced more by how a premature infant is fed than by what he is fed.

Milk feedings are started after it has been demonstrated that the infant can tolerate clear fluids. In most clinics, it is customary to start with dilute formulas and to increase the concentration gradually during the first few days. When we start milk feeding, we routinely use a stock formula containing 0.9 calorie per cubic centimeter (27 calories per ounce). This has simplified the preparation of the formula, and it has not caused any recognizable ill effects. The full requirement of 120 calories per kilogram of body weight usually can be reached when the infant is between 7 and 10 days old, although it occasionally takes more than two weeks. The rapidity with which this requirement is approached is guided entirely by the tolerance of each infant. The increase in weight is recorded on a graph (figure 2).

Vitamin supplements are started on the seventh day. A multivitamin preparation is commonly used, although vitamins C and D are the only supplements definitely required. The daily administration of 1000 units of vitamin D is sufficient to prevent clinical rickets. If premature infants are fed a diet that is high in protein, they do not completely oxidize the amino acid tyrosine unless 50 mg. of vitamin C is administered daily. No deleterious effects have been observed from these intermediate oxidative products. However, vitamin C is needed for its antiscorbutic action.

Anemia—Anemia occurs so frequently among premature infants that it may appropriately be discussed with routine care. The premature infant will tolerate an extremely low concentration of hemoglobin in the blood. We do not transfuse unless such symptoms as anorexia and sluggishness develop. These symptoms usually do not occur unless the value for the hemoglobin drops to 6 or 7 gm. per 100 cc. The response to the transfusion of 15 to 20 cc. of blood per kilogram of body weight is dramatic. In the presence of certain complications, e.g., congenital heart disease, it may be advisable to maintain a higher concentration of hemoglobin.

The administration of iron does not prevent the decrease in the concentration of hemoglobin that occurs during the first two or three months of life. However, after the infant is three months old, iron deficiency anemia may develop unless supplementary iron is administered. When the infant is three months old,

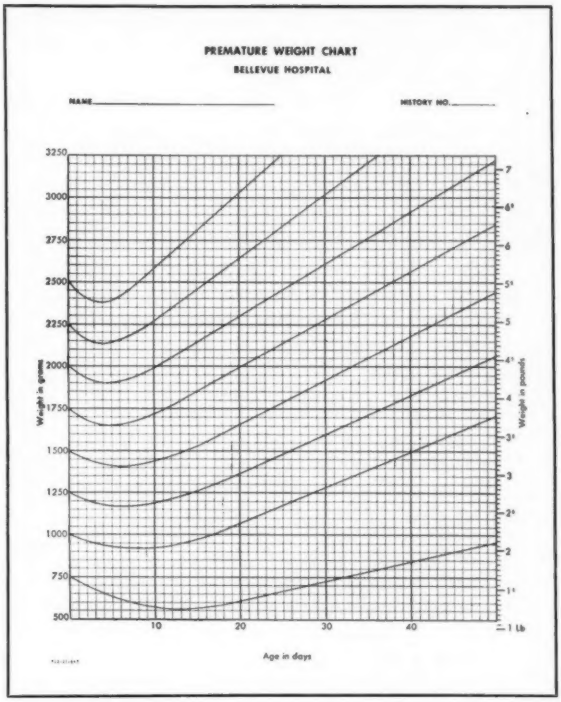

FIGURE 2. Graph for recording the weight of premature infants.

(Dancis, J., O'Connell, J. R. and Holt, L. E., Jr.: A grid for recording the weight of premature infants. J. Pediat. 33:570 [November] 1948.)

we start the daily administration of ferrous sulfate in doses of from 50 to 70 mg. of elementary iron.

Edema—The premature infant is normally born with a slight degree of edema, which is evidenced by the rounded limbs and by obliteration of the normal concavity of the palms. This usually disappears in the first few days of life. Excessive edema may reflect a more serious disturbance. It is not uncommon for the edema to recur when the infant is about three to five weeks old. The edema may be so mild that it is evidenced only by an unexpected increase in weight. Careful examination may detect a pitting edema over the tibia. The cause of this secondary accumulation of water is probably an overloading of the kidneys as a result of the increased oral intake. It does not cause any symptoms, and it disappears spontaneously in a few or several weeks. It will disappear in 24 to 48 hours if the intake of sodium is lowered. This can be done by substituting LONALAC® for the infant food that is being used.[2]

Complications

I shall consider some of the complications that have a peculiar tendency to occur in the premature infant. It must not be forgotten, however, that most of the complications that occur in a full-term infant are likely to occur in a premature infant.

Respiratory failure—Many premature infants die of respiratory failure. This complication is due to various and multiple causes, such as obstetric anesthesia and narcosis, antepartum or intrapartum anoxia, birth trauma, infection, immaturity of the respiratory center and lungs, pneumothorax, paralysis of the diaphragm and diaphragmatic hernia. Treatment should be instituted promptly, but the underlying causes should be sought and treated if possible. Clinically, the respiratory failure may be of three types: (1) The infant may fail to breathe at birth; (2) the respiratory distress may begin at or shortly after birth, and (3) transient episodes of cyanosis or apnea may occur.

If the infant fails to breathe at birth, the nasopharynx is gently cleared by aspiration, and the stomach also is aspirated (table 4). Relatively little fluid (less than 10 cc.) usually is obtained from the stomach. The chief value of these procedures probably is to exclude the presence of tracheo-esophageal fistula and atresia. If more than 15 cc. of fluid is obtained from the stomach, it constitutes strong presumptive evidence of intestinal obstruction. If breathing does not start after these procedures have been used, a small pharyngeal airway is inserted, and oxygen is administered intermittently under positive pressure (10 cm. of water). The heart rate is watched by a second physician. Although this oxygen pressure may not be sufficient to expand the lungs, the heart rate frequently increases, and the infant takes his first gasp. This may be due to reflex stimulation by the intermittent administration of oxygen under positive pressure, or it possibly may be the result of slight absorption of oxygen despite the unexpanded lungs. In the very small group of infants who do not begin to breathe after these procedures have been employed, laryngoscopy is indicated. Suitable equipment and a person skilled in its use are necessary. The respiratory passages are rapidly sucked clear, a rubber catheter is inserted between the vocal cords, and the administration of oxygen is continued under positive pressure. If the apnea still persists, the only approach left is the intermittent application of short blasts of oxygen under high pressure (up to 40 cm. of water). This must at present be considered an experimental procedure, although the results have been very promising.

Respiratory distress which begins at or shortly after birth is a much more frequent

TABLE 4

ROUTINE FOR RESUSCITATION IN THE DELIVERY ROOM*

1. Aspirate nose, throat and stomach
2. Insert pharyngeal airway, and administer oxygen intermittently under positive pressure (10 cm. of water)
3. Aspirate trachea with a laryngoscope
4. Insert a rubber intratracheal catheter, and continue the administration of oxygen under positive pressure

*The great majority of infants will start breathing before the entire routine is completed.

cause of death than the apnea which is present at birth. The newborn infant, usually a premature infant weighing between 1 and 2 kg., starts breathing spontaneously or after resuscitative measures have been used. However, evidence of respiratory distress soon is noted. Breathing is rapid and labored. The chest often is overexpanded, inspiratory retraction is evident, and cyanosis may be present. The condition may progress for hours or days. Death or recovery occurs in the first five days of life, but the infants usually recover. In the cases in which death occurs, pulmonary atelectasis is present, a variable amount of eosinophilic-staining material is found in the lungs (hyaline membrane), and the lungs usually are severely congested. The pathologic physiology involved in this syndrome is being investigated thoroughly in several clinics. The accumulating data suggest that whereas the initial pathology may be pulmonary, the cardiovascular system is rapidly involved. Changes in pressures may result in a right-to-left shunt through the still patent ductus arteriosus, which greatly aggravates the anoxia. Right-sided heart-failure may occur.

The treatment of this condition is largely expectant. The infant is placed in oxygen and high humidity and is given antibiotics. The value of digitalis is being explored.

In the type of respiratory failure that is characterized by transient episodes of apnea, the clinical picture is as follows. A particularly premature infant appears to be doing rather well, but after a period of hours or days he has a sudden attack of apnea, which commonly follows a feeding. The infant responds readily to simple therapeutic measures, but other more resistant attacks occur, and the infant finally dies. Some infants die in the course of the first attack, but others survive repeated attacks without obvious ill effects. The cause of the attacks is unknown. The fact that they occur most often in very premature infants suggests that they may be related to the immaturity of the respiratory center. The etiologic role of a reflex vagal mechanism is suspected because the attacks frequently follow a feeding.

The treatment of this type of respiratory failure is very limited. The nose and throat are aspirated, and 16 mg. of caffeine and sodium benzoate is administered subcutaneously. If the infant does not respond, the nurse inserts a pharyngeal airway and then rocks him (Eve's method). The physician subsequently may administer oxygen intermittently under positive pressure by means of a mask or an intratracheal catheter. It is important that treatment should be instituted promptly. Secondary atelectasis occurs soon after respiration stops, and experimental data indicate that the collapsed lungs are more difficult to expand than are those that have never been expanded. In an attempt to prevent subsequent attacks, the infant is placed in oxygen and a high humidity, and the volume of the feedings is reduced.

Intracranial hemorrhage—Bleeding as a result of trauma (laceration of the tentorium, subdural hematoma) occurs less frequently in premature infants than it does in infants who are born at full term. In premature infants, intracranial bleeding usually results from poorly supported subependymal vessels which rupture into the ventricles. This type of hemorrhage is peculiar to the premature infant, and is believed to be related to anoxia rather than to trauma. The symptoms are not characteristic. They include lethargy, poor feeding, respiratory distress and cyanosis. Vomiting, convulsions and rigidity occur less frequently.

The treatment of this complication is symptomatic. Lumbar puncture usually is not performed to verify the clinical suspicion of the presence of this complication because the results of this diagnostic procedure often are difficult to interpret. The spinal fluid of premature infants routinely is xanthochromic during the first weeks of life. The presence of gross blood in the spinal fluid may be due to trauma caused by the puncture. A few erythrocytes commonly are found in the spinal fluid of newborn infants who appear to be perfectly normal. In addition, the results of examination of the spinal fluid do not alter the therapeutic approach, and the manipulation incident to the puncture is undesirable.

Retrolental fibroplasia—Figure 3 shows the number of cases of retrolental fibroplasia that

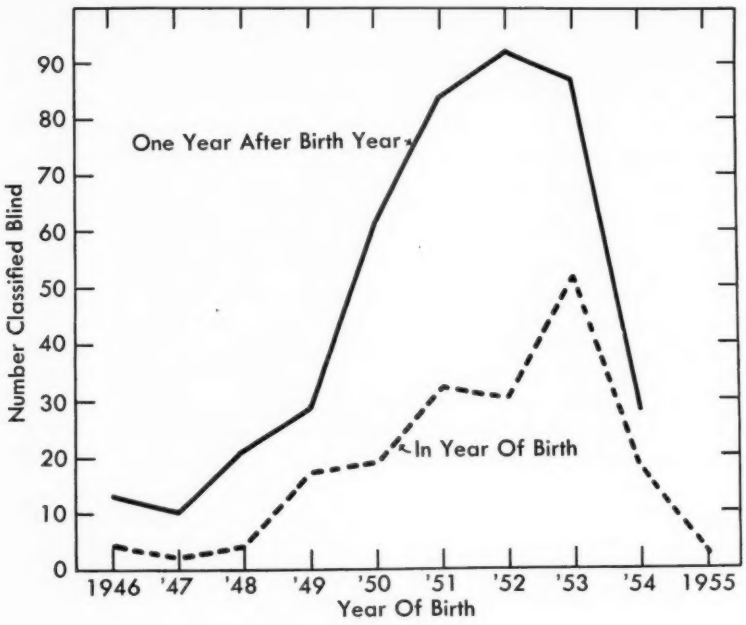

FIGURE 3. Number of cases of retrolental fibroplasia in New York State by year of birth and year classified blind, 1946-1955.

(Yankhauer, A., Jacobziner, H. and Schneider, D. M.: Rise and fall of retrolental fibroplasia in New York State. New York State J. Med. 56:1474 [May 1] 1956.)

were reported in New York State in the years 1946 to 1955 inclusive. The only therapeutic approach to this complication is its prevention. Since we have been carefully restricting oxygen therapy as described under the heading "Routine care," we have not observed any case of this complication at the Bellevue Hospital. There are some reported cases in which this complication undoubtedly has occurred despite rigid control of oxygen therapy, but such cases must be rare. Careful inquiry often will reveal some break in the technic.

The question arises as to whether exceptions should be made in the routine for oxygen therapy, that is, should the oxygen content of the incubator be raised to whatever level is necessary to relieve respiratory distress? Theoretically, if the toxic effects of oxygen result from excessive oxygen in the blood, the oxygen content of the incubator cannot be too high so long as cyanosis is present. There is no evidence on this point. The practical difficulty lies in the subjective nature of the evaluation of cyanosis. This approach to oxygen therapy would seem particularly dangerous in cases of respiratory distress without cyanosis. In most of these cases, a hyaline membrane is present, and the respiratory difficulty frequently does not respond to any concentration of oxygen. It may be possible to approach these cases more rationally when instruments become available for the accurate measurement of the oxygen tension or content of the infant's tissues. At present, we rarely deviate from our rigid policy of oxygen control. We prefer to avoid a known risk of considerable magnitude although we possibly may sacrifice the unevaluated benefits of a more flexible approach.

Hemolytic disease of the newborn—When hemolytic disease of the newborn occurs in a premature infant, it is considered to be an absolute indication for exchange transfusion because kernicterus frequently is associated with this complication.

Kernicterus—Recently, this complication has been reported in premature infants in the absence of hemolytic disease. Few statistical data are available. Its incidence has been reported to be about 1 per cent among all premature infants who are admitted to the hospital and about 5 per cent in cases in which

necropsy is performed on premature infants.

The clinical picture usually includes some evidence of distress, such as episodes of apnea and cyanosis and difficulty in feeding, during the first few days of life. About the fifth day, coincident with the development of severe jaundice, intermittent episodes of hypertonicity and opisthotonos occur. During these episodes, the arms and legs are extended. These episodes may be mild, and their presence may be missed. Although death may occur in 24 to 48 hours, the infant may survive, and deafness, mental retardation and athetosis may become evident at a much later date.

Much of the thinking regarding this complication is based on experience gained with erythroblastosis fetalis. In some medical centers, exchange transfusion is being recommended for all infants in whom the concentration of bilirubin is more than 18 mg. per 100 cc. of serum. There are several reasons for questioning whether the comparison with erythroblastosis fetalis is valid. First, the most important thing that exchange transfusion accomplishes in cases of hemolytic disease is the removal of iso-immunized cells. Probably only 5 to 10 per cent of the bilirubin is removed by an ordinary exchange transfusion, and the concentration of bilirubin will return to its former high level in a few hours. Thus, if hemolytic disease is not present and if treatment is directed only against the hyperbilirubinemia, there is likely to be a need for serial exchange transfusions unless liver function should improve abruptly. This exaggerates the existing technical problems. In a small premature infant about five days old, the umbilical vessels usually are no longer available for transfusion. There is the basic and still unsolved problem of how important the hyperbilirubinemia is in the production of the kernicterus. In many cases, there is evidence of serious illness before the jaundice appears.

In England, the high incidence of kernicterus in some clinics has been attributed to the administration of excessive amounts of vitamin K (30 to 50 mg. instead of the indicated 1 or 2 mg.). The administration of large doses of this vitamin appears to produce hyperbilirubinemia. In this country, the increased incidence of kernicterus has been specifically attributed to routine prophylactic use of GANTRISIN® in spite of a relatively low concentration of serum bilirubin. Marked hyperbilirubinemia occasionally occurs in infants who do not have any evidence of kernicterus. Because of these considerations, we do not treat hyperbilirubinemia of premature infants with exchange transfusions. However, more information is badly needed before definite decisions can be made.

Infection—The prevention of infection is important, but the approach to this problem has changed in recent years. It is now recognized that contact is the most important means of spreading infection, and hand washing is stressed. Most institutions no longer require their nurses to wear masks, and many have given up the individual gown technic. This technic is still required of personnel, e.g., physicians, who are not assigned solely to the premature unit.

The routine prophylactic use of antibiotics has not been evaluated. We use antibiotics only when we believe that they are definitely indicated. However, because of the paucity of symptoms among premature infants, the indications are far more lenient than elsewhere in the hospital.

Antibiotics are used prophylactically for infants born more than six hours after rupture of the membranes, and for infants with respiratory distress. Overt infections, of course, are treated vigorously, but even unexplained sluggishness, anorexia or loss of weight in an infant who previously was doing well is considered an adequate indication for the use of antibiotics. Diagnostic measures, at least a blood culture and other procedures suggested by the results of examination, are used, and the administration of antibiotics is begun. A broad-spectrum antibiotic is indicated because of the nature of the pathogens commonly encountered in the premature unit. We have used a combination of procaine penicillin and chloramphenicol. One hundred and fifty thousand units of procaine penicillin is administered twice a day, and 50 mg. of chloramphenicol per kilogram of body weight is administered daily in four divided doses.

Dismissal

Most premature infants are dismissed from the hospital when they have attained a weight of 2250 to 2500 gm. This policy may be altered in either direction depending on the progress of the infant and on the evaluation of the care available at home.

The problems presented by a premature infant do not end when he is dismissed from the hospital. The handicaps of weight and height usually are overcome by the time the infant is one or two years of age, although a longer time may be required. Respiratory infections, including pneumonia, remain a hazard during the first few years of life. Potentially more crippling are the emotional problems resulting from the prolonged separation of the child and the parents, and the apprehension of caring for a "delicate" premature infant. Parents need considerable support from the physician while they are adjusting to their new responsibility. It now is becoming customary in many medical centers to invite the parents to the hospital for instruction. They are permitted to feed and care for their child before the time of his dismissal.

Comment

The problem of premature birth has increased and will continue to increase because of the major advances being made against other leading causes of death, notably infectious diseases. The outlook for the premature infant has improved in recent years, primarily because of better nursing care, increased understanding of nutritional requirements, and the control of infection in premature units. The eventual solution of the problem of prematurity undoubtedly lies in the prevention of premature birth. In the meantime, the outstanding problem in the premature unit is the infant who usually weighs less than 1500 gm. at birth and who dies in the first few days of life with clinical signs of respiratory failure.

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Recent Developments in the Study of Hereditary Diseases in Children

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In the last few years, a number of new approaches have been developed for studying diseases which are primarily hereditary in origin. These have been effective in bringing genetics much closer to clinical medicine, so that, today, the practicing physician has occasion to use these new tools for the diagnosis and treatment of such conditions. The purpose of the present paper is to discuss four such approaches, and to illustrate each with an example drawn from pediatrics.

Study of Pathogenesis

From the beginning, doctors have always been fascinated by the mechanisms responsible for the so-called inborn errors of metabolism. As early as 1908, Sir Archibald Garrod[1] suggested that these conditions occurred as a result of blocks in the normal pathways of metabolism:

> It may well be that the intermediate products formed at the several stages have only momentary existence as such, being subjected to further changes almost as soon as they are formed, and that the course of metabolism along any particular path should be pictured as in continuous movement rather than as series of distinct steps. If any one step in the process fails, the intermediate product in being at this point of arrest will escape further change, just as when the film of a biograph is brought to a standstill, the moving figures are left foot in air. All that is known of metabolism tends to show that in such circumstances, the intermediate product is being wont to be excreted as such rather than it is further dealt with along abnormal lines. . . .

He postulated that such metabolic blocks occurred as a result of deficiencies of specific enzymes:

> Nowadays, very different ideas are in the ascent. The concept of metabolism in block is

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> giving place to that of metabolism in compartments. The view is daily gaining ground that each successive step in the building up and breaking down, not merely of proteins, carbohydrates, and fats in general, but even of individual fractions of proteins and of individual sugars is the work of special enzymes set apart for each particular purpose. . . .

Garrod was far ahead of his time. It has taken nearly half a century of continuous progress to confirm his hypothesis which can be illustrated in the example on galactosemia which follows:

About 50 years ago, the German physician von Reuss reported the case of an eight month old infant with marasmus and melituria. The melituria disappeared when milk was eliminated from the diet, but the infant died before further tests could be performed. Subsequently, other such cases were found. In each instance, the infants appear normal at birth, but after a few days of milk feeding, they start to vomit, become lethargic and fail to gain weight, and an enlargement of the liver becomes apparent. Ascites and edema may develop, and, if the condition is severe, death occurs due to malnutrition and wasting. Infants who survive are usually malnourished and dwarfed at two or three months of age, and mental retardation and cataracts may be discerned. In others, cirrhosis of the liver may develop months or years after the acute phase of the disease. In all instances, the signs and symptoms regress after the deletion of milk and milk products from the diet.

Although pediatricians have been familiar with the disease for some time, it is only in the past few years that its familial nature has been properly recognized. In looking back over the reported cases, it would appear that two or more children were involved in nearly half of the families. The condition appears to be transmitted as a simple recessive, but the incidence of the abnormal gene in the population is not known at the present time.

The exact cause of the disease has only been clarified as a result of investigations carried on by scientists in different parts of the world. From the beginning, it was known that the sugar present in the urine of such infants was not glucose. However, it was difficult to identify the specific sugar at fault. The development of paper partition chromatography technics by English workers 10 years ago made the diagnosis easier. In the meantime, it became known that excessive amounts of galactose were present in the blood of infants with this disease, and physicians were able to do galactose tolerance tests on infants they suspected had the disease.

For many years, it was thought that galactosemia represented a congenital defect of the liver in which the conversion of galactose into glycogen was in some way damaged. Its frequent appearance within certain families suggested that some enzyme might be at fault. However, nothing could be done about it because the normal pathways of galactose metabolism were not known. In the late 1940s, a series of brilliant studies by LeLoir and his

TABLE 1

NORMAL PATHWAY OF GALACTOSE METABOLISM*

1. Galactose + ATP $\xrightarrow{\text{GALACTOKINASE}}$ Galactose-1-PO_4 + ADP

2. Galactose-1-PO_4 + Uridine diphosphate glucose $\xrightarrow{\text{P-GAL-URIDYL-TRANSFERASE}}$ (X) Glucose-1-PO_4 + Uridine diphosphate Galactose

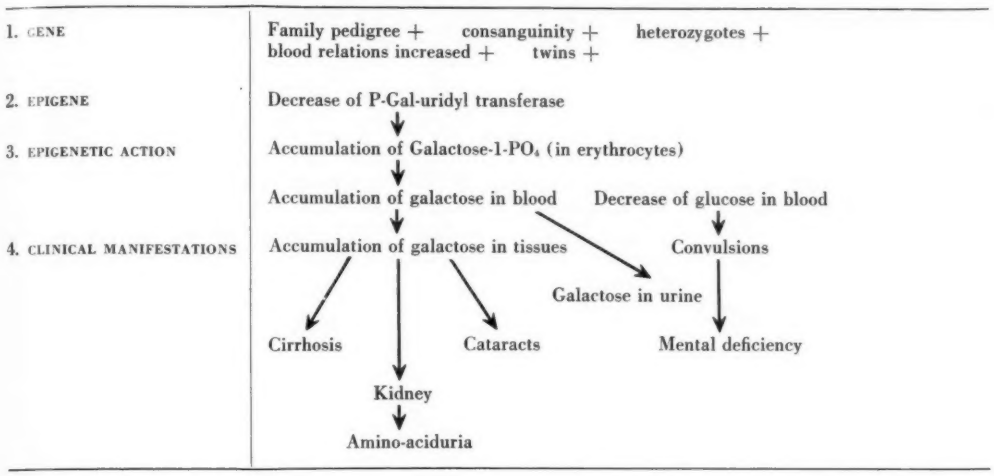
3. Uridine diphosphate Galactose $\xrightarrow{\text{GAL-WALDENASE}}$ Uridine diphosphate Glucose

4. Uridine diphosphate glucose $\xrightarrow{\text{PP URIDYL TRANSFERASE}}$ Uridine triphosphate + Glucose-1-PO_4

*The enzymes for each step are shown in capital letters. The metabolic block in galactosemia is marked by a cross (X).

TABLE 2

PRESENT CONCEPTS OF PATHOGENESIS OF GALACTOSEMIA



co-workers[2] in Argentina culminated in the knowledge that galactose was converted to glucose-1-PO_4 in a series of four separate steps as shown in table 1. They also showed that each step was catalyzed by a specific enzyme, whose name is given in capital letters between the reactions.

It now only remained to find out which of the steps might be blocked. In 1955, Schwarz, Goldberg, Komrower and Holzel[3] in Manchester, England, showed that when milk was given to a galactosemic child there was an abnormal accumulation of galactose-1-PO_4 in the red cells, while this metabolite was not present in normal children. This meant that the block must occur somewhere beyond galactose-1-PO_4, and that galactokinase, the enzyme needed for the first reaction, was present in adequate amounts. In 1956, Isselbacher, Anderson, Kurahashi and Kalckar,[4] working in the United States, demonstrated that Gal-waldenase and PP uridyl transferase, the enzymes needed for the third and fourth steps, were present in normal amounts in the erythrocytes of galactosemic children. However, P-Gal-uridyl transferase, the enzyme needed for the second step, was barely detectable in 10 such children. From this, they concluded that galactosemia occurs as a result of an enzyme deficiency which causes a metabolic block in step 2, and that all other pathways of metabolism in such patients are normal and intact.

One might conveniently summarize the present concepts of the disease in a diagram as illustrated in table 2. First, it is necessary to show that galactosemia is a genetic disorder. This is suggested by: (1) the presence of the disease in several members of the family, (2) an increased incidence of the disease among blood relations, (3) frequent occurrence of the disease among cousin marriages, (4) occurrence of the condition in both twins when they are identical, and (5) detection by chemical means of the heterozygous carrier of the abnormal gene. All this provides suggestive evidence. However, this type of information must of necessity be indirect, and is not something that one can directly measure in a test tube or under a microscope.

It is possible to measure the absence of the enzyme P-Gal-uridyl transferase chemically. This, therefore, is the first effect of the gene which can be seen, and which might be called the epigene. All of the clinical signs and symptoms of the disease must directly result from this disturbance of the epigene. In the case of galactosemia, this results in an accumulation of galactose-1-PO_4 in erythrocytes, and this in

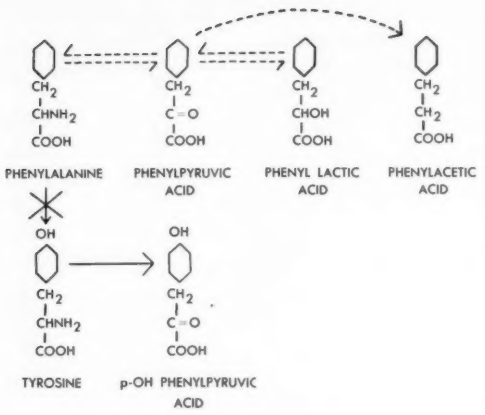


FIGURE 1. Normal pathway of phenylalanine metabolism. The metabolic block in phenylketonuria is marked by a cross (X).

turn causes an abnormal accumulation of galactose in both the blood and tissues. This also results in the spilling over of galactose into the urine. The excessive galactose content of the liver and damage to the renal tubules cause the excessive excretion of amino acids into the urine. There is also some evidence to suggest that the excessive galactose levels in the blood depress the blood glucose levels, and this in turn causes convulsions, and possibly mental retardation. Thus an obscure syndrome of marasmus and melituria in infancy, certainly not an uncommon finding in the early part of this century, has now been shown to result from an abnormality of a single gene and a single enzyme in the body.

Detection of Carriers (Heterozygotes)

Recent improvements in technics have made it possible to detect carriers of abnormal genes. This can be illustrated by some of our own work on phenylketonuria.

Phenylketonuria is a hereditary disease which was first described in 1934 by Folling, a Norwegian biochemist. He showed that a group of mentally deficient patients could be distinguished from other ones by the presence of phenylpyruvic acid in the urine. Since then, several hundred such patients have been discovered in different parts of the world, and it is believed that this disease occurs once in every 40,000 births in the United States.

Clinically, the patients appear to be ordinary imbeciles. However, certain features about them permit an experienced physician to establish the diagnosis even before the urine has been tested. In the first place, they tend to show more normal physical development than nonphenylketonurics of a comparable mental level. Gross physical defects are seldom found. Many of the children are fair skinned and have blond hair and light blue eyes, and it is not unusual for phenylketonuric children to be singled out for their attractive features during early infancy. Their skin is sensitive, and eczema is a frequent finding.

The metabolic block in phenylketonuria is shown in figure 1. In the normal person, phenylalanine is converted to tyrosine, which in turn is converted to p-OH phenylpyruvic acid, and so on, until acetoacetate becomes the end product. In phenylketonuria, the enzyme responsible for the first step, phenylalanine hydroxylase, is defective. As a result, phenylalanine accumulates in the blood and is converted to phenylpyruvic acid, phenyl lactic acid, and phenylacetic acid, which are excreted through the urine.

Phenylketonuria is transmitted as a rare recessive. The mode of inheritance can be illustrated in the hypothetical family shown in figure 2. Let us assume that two normal individuals, whom we might call Adam and Barbara, are mated and have four children whom we shall call Charlotte, David, Ellen and Frank. We find that Charlotte excretes phenylpyruvic acid in the urine and must, therefore, be a phenylketonuric with two abnormal genes. She must have inherited one of these from her father, Adam, and one from her mother, Barbara. Since both her parents are superficially normal and do not excrete phenylpyruvic acid in the urine, they must each possess one normal and one abnormal gene for phenylketonuria and are, therefore, heterozygous carriers of that abnormal gene. Assuming normal distribution, when two such individuals mate, one would expect them to have one affected child (Charlotte), two carriers like themselves

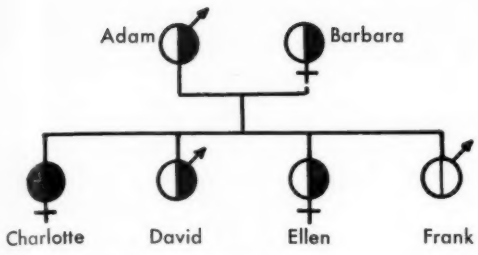


FIGURE 2. Family tree illustrating the recessive mode of inheritance.

(David and Ellen), and one completely normal child (Frank).

Geneticists have always described this as a recessive mode of inheritance because these carriers of the abnormal trait appear to be normal in every way. In the case of phenylketonuria, Adam, Barbara, David and Ellen are not feebleminded, do not excrete phenylpyruvic acid, and cannot be distinguished from Frank. Yet, genetically speaking, they are quite different from Frank.

Phenylketonuria, like galactosemia, occurs as a result of an enzyme defect. When one of the two genes is abnormal, one expects a partial defect in the phenylalanine hydroxylase enzyme system. This defect is apparently too slight to be manifest while the patient is on a regular diet, because the plasma phenylalanine and urine phenylpyruvate excretion is exactly the same as that of normal individuals. However, if a strain is put on the phenylalanine system by giving a sudden load, the weakness may show up. Accordingly, Driscoll, Troll, Knox and I[5] gave 0.1 gm. of phenylalanine per kilogram of body weight by mouth to parents of known phenylketonurics and followed their plasma phenylalanine levels for one, two and four hours. The same test was done on a comparable group of normal controls. The results of these studies are shown in figure 3. It can be seen that the carriers (heterozygotes) had plasma phenylalanine levels which were twice as high as those of the controls in all three study periods. Actually, there was remarkably little overlap, so that between 85 and 90 per cent of the carriers could clearly be distinguished from normal individuals.

This type of study is of theoretical interest because it provides further confirmation that a decrease of phenylalanine hydroxylase is the primary defect in phenylketonuria, and of practical importance because one can predict ahead of time which type of matings may result in a phenylketonuric child.

In a recent survey, it was found that carriers can be detected in 28 of 36, or about three-fourths of the hereditary diseases of a biochemical nature.[6]

Linkage

I shall discuss a rather different method for studying heredity in medicine. It is now generally agreed that the genes responsible for various characteristics are carried on 23 pairs of chromosomes in man. Quite a bit is known about the genes which lie on the XY pair of sex chromosomes. Such conditions as hemophilia, agammaglobulinemia and color blindness are carried on that pair, and the disease process is transmitted from an affected male in the first generation through an unaffected female in the second generation to an affected male in the third generation. However, much less is known about the genes on the remaining 22 pairs of chromosomes. As a matter of fact, it is not even known what characteristics are carried on which chromosome. The discovery of the blood groups has greatly increased the impetus to this type of work, since they are constant characters which do not

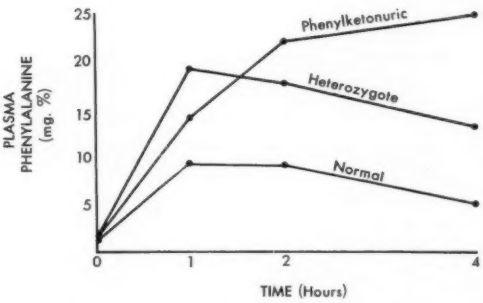


FIGURE 3. Phenylalanine tolerance tests on parents (heterozygotes) of phenylketonurics as compared with normal controls. The curve of a phenylketonuric is also shown for comparison.

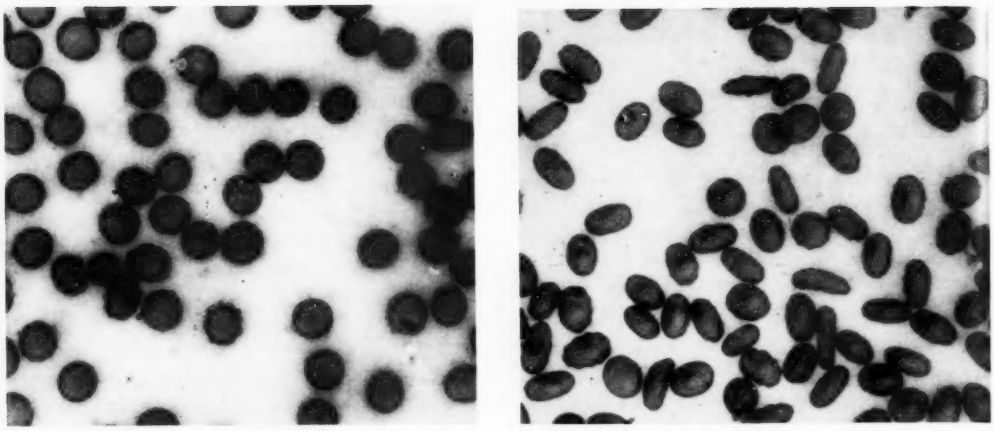


FIGURE 4. Blood smears of normal adult *(left)* and patient with elliptocytosis *(right)*.

(Godall, H. B., Hendry, D. W. W., Lawler, S. D. and Stephen, S.A.: Data on linkage in man: Elliptocytosis and blood groups: Family 3. Ann. Eugenics 17:272 [April] 1953.)

change in the lifetime of an individual and hence can be used as markers.

Oval or elliptically shaped erythrocytes normally occur in the camel and llama, but are comparatively unusual as a hereditary trait in man. When they do occur (as illustrated in figure 4), the affected individuals may be divided into three groups: (1) hereditary elliptocytosis with no signs of hemolysis; (2) hereditary elliptocytosis with hemolysis, but no anemia, a compensated hemolytic disease (the patients may have splenomegaly, reticulocytosis, icterus and increased fecal urobilinogen), and (3) hereditary elliptocytosis with hemolytic disease and anemia. In about 12 per cent of all cases, the patients belong to the last two groups.

Hereditary elliptocytosis is transmitted as an autosomal dominant; that is to say, the clinical picture will appear when one individual has one abnormal and one normal gene for the condition. It is transmitted directly from parent to child.

In 1954, Lawler and Sandler[7] showed that the trait for elliptocytosis was linked with that of the Rh blood groups. In seven families, they found that the specific Rh group and elliptocytosis were transmitted together from one generation to another 66 times and were not transmitted together 7.5 times. This means that most probably the two genes are located on the same chromosome and are not too far apart in position on that chromosome. However, they are not likely to be next to each other, since in 10 to 15 per cent of cases they were not transmitted together.

It is apparent that eventually it will be possible to make a map of the chromosomes showing the relation of the various genes to each other. This has been done in the fruit fly by breeding experiments, and can be done in man as more examples of this type of linkage relationship are found.

Treatment of Hereditary Diseases

Until recently, physicians have taken a pessimistic view of diseases which are genetically determined, because they felt that it would be impossible to correct a defect within the cell itself which was transmitted from one generation to another. Today, this attitude is no longer justified because therapy is available in a number of ways.

Supportive treatment—Although there is no cure for such conditions as sickle cell anemia and congenital hemolytic icterus, patients with these diseases can frequently be made to lead a more normal life by supportive therapy, such as blood transfusions and splenectomy. The use of antibiotics in cases of cystic

fibrosis of the pancreas is another example.

Substitution therapy—When the exact metabolic defect is known, substitution therapy can be most effective. For example, children with afibrinogenemia and agammaglobulinemia can be given regular transfusions of the missing protein fraction. Others with endocrine disorders, such as diabetes mellitus or the adrenogenital syndrome, can be successfully treated with appropriate hormone preparations.

Withdrawal therapy—Conditions resulting from a deficiency or absence of a specific enzyme have been the most difficult to correct. The enzymes usually work inside the cell. As a result, the injection of a purified preparation of the enzyme, even if available, would not be useful in bringing about a normal metabolic pattern. However, one can sometimes prevent the damage done by the toxic substance, which accumulates as a result of the failure of the missing enzyme to function, by withdrawing it from the diet altogether. This was first successfully done in galactosemia, and has recently been done in phenylketonuria.

In 1953, Bickel, Gerrard and Hickmans[8] made the assumption that the excessive concentration of phenylalanine or perhaps of one of the breakdown products of phenylalanine (figure 1) might be responsible for the mental deficiency in phenylketonuria. They prepared a special diet which contained all of the essential amino acids but was low in phenylalanine, and gave it to a patient with phenylketonuria. The result of such a diet on plasma phenylalanine, urine phenylalanine, and urine phenylpyruvate levels is shown in figure 5, which was made in one of our own cases. It can be seen that the withdrawal of phenylalanine from the diet was effective in bringing all these substances down to the same levels as those in a normal person.

The critical test of the value of such a diet is whether normal mental development can occur in a phenylketonuric patient. It is still too early to draw any final conclusions since much of the work in England and America

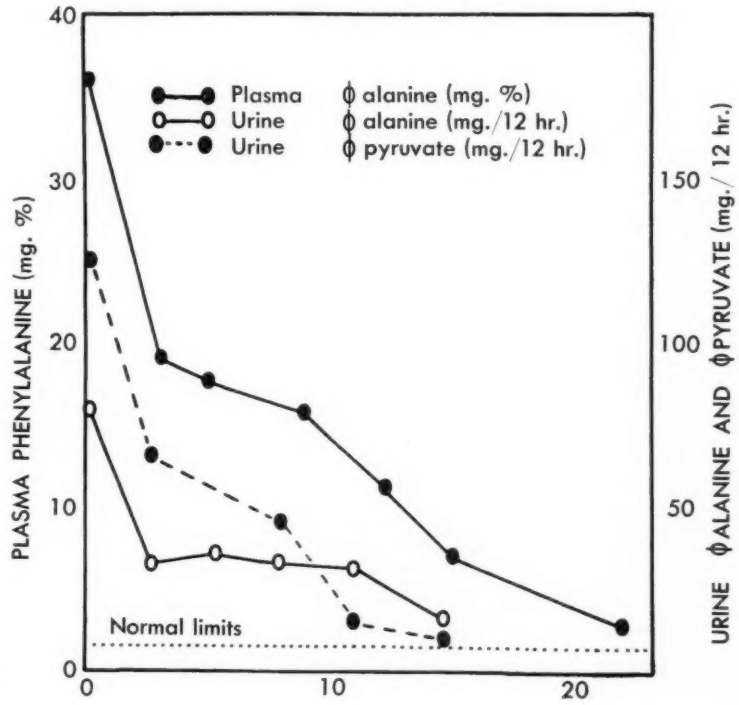


FIGURE 5. Effect of a phenylalanine-free diet on the plasma and urine in a case of phenylketonuria.

is still in progress. However, it is safe to say that the diet definitely has no effect on mental development after the age of six years, and probably does have a definite effect in patients under six, with the effect being more marked in the youngest age groups.[9] I am aware of at least three cases in which the patients have been treated since six weeks of age. Two are entirely normal and the third is nearly so one year or longer after the start of treatment. One should be cautious about assessing intelligence in cases of phenylketonuria because, in a random sample, about 1 per cent of all the patients have an I.Q. of 70 or higher. Assuming that to be the case, the probability of the first such case being one of the atypical ones with normal intelligence is 1 in 100, the probability of the second one being so is $(1 \text{ in } 100)$,[2] and that of the third being so is $(1 \text{ in } 100)^3$ or 1 chance in 1,000,000. In other words, there is very little possibility that these three children developed normal intelligence by chance alone.

Comment

It is hoped that this short discussion on some of the newer approaches to hereditary diseases will stimulate practicing physicians to take a greater interest in these problems. It is further hoped that when they do encounter a condition which affects several members of a family, they will call it to the attention of one of the clinics doing work on human heredity so that proper studies of the type described can be undertaken to increase our future knowledge of human genetics.

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Books Received

Books received are acknowledged, and, as space permits, those of principal interest to our readers are reviewed more extensively. Reviews appear in this issue starting on page A-104; additional listings are on pages 232, 298 and A-112.

The Specialties in General Practice. Edited by Russell L. Cecil, M.D., Professor Emeritus of Clinical Medicine, Cornell University Medical College, New York City, and Howard F. Conn, M.D., Fellow, Department of Physiology, Baylor University College of Medicine, Houston. Ed. 2. 780 pages, illustrated. 1957, W. B. Saunders Company, Philadelphia and London. $16.00.

Management of the Patient With Headache. By Perry S. MacNeal, M.D., Physician to Pennsylvania Hospital and Benjamin Franklin Clinic, Bernard J. Alpers, M.D., Professor and Head of the Department of Neurology, Jefferson Medical College of Philadelphia, and William R. O'Brien, M.D., Psychiatrist and Head of the Department of Psychiatry, Pennsylvania Hospital, Philadelphia. 145 pages. 1957, Lea & Febiger, Philadelphia. $3.50.

The Compleat Pediatrician. For the use of general practitioners, pediatricians, interns and medical students. By Wilburt C. Davison, M.D., James B. Duke Professor of Pediatrics, Duke University School of Medicine, Durham, North Carolina, and Jeana Davison Levinthal, M.D., Instructor in Pediatrics, University of Michigan School of Medicine, Ann Arbor. Ed. 7. 257 pages. 1957, Duke University Press, Durham. $4.25.

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Brain Mechanisms and Drug Action. A symposium: Fourth annual scientific meeting of the Houston Neurological Society, Texas Medical Center, Houston. Compiled and edited by William S. Fields, M.D., Professor of Neurology, Baylor University College of Medicine, Houston. 147 pages, illustrated. 1957, Charles C Thomas, Springfield, Illinois. $4.25.

Infantile Cortical Hyperostosis

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INFANTILE cortical hyperostosis, frequently referred to as Caffey's disease, is a disease peculiar to infants and characterized by swelling over the bones of the jaw, thorax or extremities; irritability; fever; a fluctuating course, and roentgenographic evidence of periosteal formation of new bone over the diaphyses of the affected bones. This disease was first described in this country by Caffey and Silverman.[1]

Incidence and Etiology

To the best of my knowledge, the literature does not contain any report of a case in which bona fide infantile cortical hyperostosis first occurred in an infant who was more than five months old. The disease, however, has been diagnosed in utero by means of prenatal roentgenography.[2] In 69 reported cases (table 1), the average age of the infants at the onset of disease was nine weeks.[3] Sex, geography and race do not influence the development of the disease. It was originally thought that Negroes were less susceptible to the disease than were white infants, but, as awareness of the disease has increased, no difference has been found in its incidence in the two races. In 28 of 32 cases observed in the Harriet Lane Home for Invalid Children in the past six years, the patients were Negro infants. This is about the same ratio of Negro patients and white patients seen in the outpatient department of The Johns Hopkins Hospital.[4] The frequency of the disease is further evidenced by the observation of 15 cases in the private practice of one pediatrician in the past six years.[5] It has occurred in several siblings and cousins, and the mother of an affected infant apparently had had the disease in infancy.

Little can be said of the etiology except that it remains an enigma. Bacterial, fungal, para-

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TABLE 1

SITE OF INVOLVEMENT IN 69 REPORTED CASES

SITE OF INVOLVEMENT	PER CENT OF CASES
Mandible	77
Tibia	44
Ulna	36
Clavicle	35
Ribs	32
Humerus	32
Femur	32
Fibula	18
Pelvis	6
Skull	3

sitic and viral agents have been sought, but there is no conclusive evidence that infection plays an etiologic role. Trauma, allergy, endocrinopathy, and dietary and other factors have proved fruitless avenues of approach to the etiology. The only suggestive leads are the familial occurrence, which is seen more and more frequently, and the evidence gained from pathologic examination. The time that has elapsed since the disease was first described and the number of cases that have been reported are not sufficient to permit a positive statement on the etiologic role of heredity.

Pathology

In discussing the pathology, the early and late lesions of the disease will be considered separately. The histologic description of an early lesion represents the only new finding in this disease in the last six years.

In a case in which biopsy was performed earlier in the course of the disease than it apparently has been in any case reported previously, the microscopic appearance of the lesion was as follows:[6] The periosteum was greatly thickened, was densely packed with fibroblasts, and contained focal collections of polymorphonuclear leukocytes. Marked edema was present, and the lesion was very vascular. The focal collections of polymorphonuclear leukocytes were widely scattered. They did not contain any necrotic debris. In the area approximating the newly formed bone, both within the haversian spaces and in the periosteum, there frequently were "foreign-body" giant cells. Many of the blood vessels in the periosteum and in the overlying muscle contained prominent endothelial cells which had rounded nuclei and cytoplasm that was more prominent than normal.

In the late stage, the disease involves the overlying soft tissues as well as the bone and periosteum. Fibrous strands extend from the periosteum to the fascia, muscle and adipose tissue. Areas of necrosis occur in the soft tissues over the involved bone. Proliferation of the intima occurs in the arteries in the lesion. The periosteum is hyperplastic and edematous. The new bone that is formed is irregular and imperfect in pattern. Hemorrhage does not occur in the lesion.

If it becomes possible to obtain a biopsy specimen from a site in which an intense reaction has not occurred, and, particularly, if it becomes possible to obtain a specimen before involvement has become apparent, additional knowledge may be gained regarding the etiology. The specimen obtained for this purpose should include the skin, adipose tissue, muscle and fascia, and periosteum and bone.

Symptoms and Laboratory Findings

In a typical case, swelling occurs suddenly over one or more bones (figure 1) of an apparently healthy infant, and is associated with irritability and fever. The fever and irritability frequently precede the swelling by days or weeks. Both of these symptoms may not be present. Pseudoparalysis may occur if the disease involves the bones of an extremity. Pleural effusion and splinting of the thorax may occur if the disease involves the ribs.

The tumors invariably are situated over bone. Erythema does not occur, and the temperature of the overlying skin is not increased. The overlying soft tissues are movable, although often less freely than normal. The tumorous areas usually are tender except in the late stages. In cases in which the disease is extensive, angular deformities of the long bones may occur, but these usually disappear spontaneously in a year or two.

Laboratory tests are of little assistance in the diagnosis. The leukocyte count and the

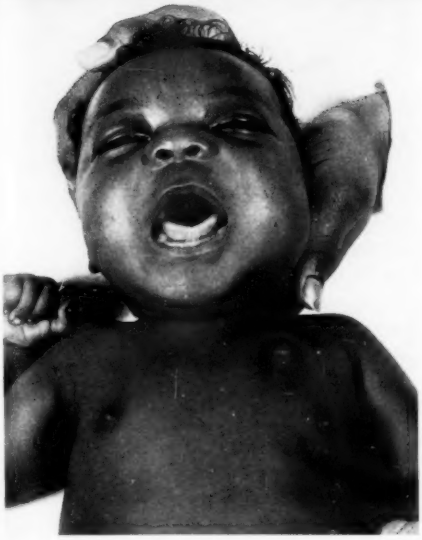

FIGURE 1. Gross swelling over the mandibles which is characteristic of infantile cortical hyperostosis.

FIGURE 2. Periosteal elevation of the right mandible and production of new bone beneath it.

FIGURE 3. Elevation of periosteum on the proximal half of the ulna. This is a very early lesion.

FIGURE 4. Marked progression of lesion shown in figure 3, and subsequent involvement of the radius.

FIGURE 5. Far-advanced lesions. The bone involved originally appears to be encased within the new bone which has formed.

sedimentation rate of the erythrocytes usually are increased. Mild anemia occurs commonly. In the early and acute stage, the concentration of serum alkaline phosphatase may be increased. Otherwise, the results of routine laboratory tests are normal.

Roentgenographic examination will confirm the clinical suspicion of the presence of the disease (figures 2 to 5). In the initial stage, it will reveal only a slight elevation of the periosteum and minimal evidence of periosteal formation of new bone along the diaphysis. Later, it will disclose evidence of periosteal osteoblastic activity. At times, the normal diameter of the bone will be tripled. When such marked activity occurs beneath the periosteum, there will be evidence of reabsorption of bone from the medullary space.

Differential Diagnosis

Infantile cortical hyperostosis must be distinguished from the following diseases:

Parotitis—If the disease involves the mandible, it may be confused with parotitis, but the diagnosis can be made by roentgenographic examination, which will reveal involvement of bone.

Syphilis—The irritability, fever and pseudoparalysis may suggest the presence of syphilis. The roentgenographic findings are different in the two diseases, and results of the serologic test will be negative in cases of infantile cortical hyperostosis.

Scurvy—Pseudoparalysis, anemia and superficial examination of the roentgenograms may suggest the presence of scurvy, but closer examination of the roentgenograms will reveal the typical changes of infantile cortical hyperostosis. Furthermore, the concentration of vitamin C in the serum is normal in this disease.

Rickets—The periosteal elevation which occurs in the early stage and the bowing which occurs in the advanced stage may be suggestive of rickets. None of the other stigmata of rickets are present in cases of infantile cortical hyperostosis, and the metaphysis is not involved.

Osteomyelitis—The presence of this disease may be suggested by the fever, leukocytosis, and swelling and tenderness over bones, and by the roentgenographic evidence of periosteal reaction. In cases of infantile cortical hyperostosis, blood cultures and cultures of material aspirated from the involved sites are negative. In the advanced stage of this disease, the roentgenographic appearance does not resemble that of osteomyelitis.

Tuberculosis—In cases of tuberculosis of bone, motion also is painful and limited, but the age of the patient and the roentgenographic appearance will distinguish the two diseases.

Poliomyelitis—In cases in which involvement of the mandible or scapula is painful and causes meningismus which is associated with fever, irritability, and perhaps with pseudoparalysis, the presence of poliomyelitis may be suspected. The cerebrospinal fluid is normal in cases of infantile cortical hyperostosis, and there is no real paralysis.

Meningitis—The presence of this disease is suggested when meningismus, fever and leukocytosis are present, but the spinal fluid is normal in cases of infantile cortical hyperostosis.

Acute rheumatic fever—Swelling and tenderness near the joints, leukocytosis, fever and elevation of the sedimentation rate may be suggestive of acute rheumatic fever, but the two diseases can be distinguished by roentgenographic examination.

Trauma—Trauma may cause a periosteal reaction, leukocytosis and elevation of the sedimentation rate. The sudden onset of infantile cortical hyperostosis may be compatible with an injury; however, there rarely is a history of an injury, and the course of this disease and that of an injury are entirely different.

Osteogenic sarcoma—The roentgenographic findings may be very suggestive of osteogenic sarcoma, which is rather rare in infants. Biopsy and the clinical course will distinguish the two diseases.

Leukemia—The mild anemia might suggest the presence of leukemia, which frequently causes a periosteal reaction, but the normal platelet count, the absence of abnormal cells in a peripheral blood smear, and the absence of splenomegaly would be strong evidence against the presence of leukemia.

Vitamin A intoxication—Vitamin A intoxication causes pain, anemia and a periosteal reaction similar to that observed in cases of infantile cortical hyperostosis. Vitamin A intoxication occurs in older patients. Leukopenia and hepatomegaly are present, the hair is coarse, and the concentration of vitamin A and carotene in the blood is normal.

Treatment and Prognosis

In the overwhelming majority of cases, the course of the disease is benign, although the infants may have rather prolonged periods of apparent discomfort and irritability when the disease is active. One of the most characteristic features of the disease is its fluctuating course. A tumor appears suddenly, but may subside in a week or more. This subsidence is followed by a variable quiescent period. The whole cycle then is repeated, and one or more different bones are involved. In a few cases, the course will be relatively mild and quite short. In these cases, the diagnosis can easily be missed if one is not aware of the possible presence of the disease.

Very rarely, the contiguous bones may be involved extensively, and fusion may result. Death of a patient with Caffey's disease has occurred and no other cause for death could be found. It should be emphasized that serious complications are very rare.

Treatment is symptomatic. Appropriate doses of aspirin should be administered to alleviate the discomfort and irritability. A mild sedative such as phenobarbital may be helpful. Small transfusions are indicated if anemia is severe.

Administration of adrenocorticotropin (ACTH) and cortisone has been tried. Because of the notoriously fluctuating course of this disease, it is extremely difficult to evaluate the results in reported cases in which this type of therapy has been used. It would be fair to state that steroid therapy should not be withheld in cases in which the patients are very ill. This type of therapy has the potentiality of preventing impending fusion between bones which are extensively involved. In a disease such as infantile cortical hyperostosis, in which the clinical course usually is benign, steroid therapy, which has attendant hazards when used for infants, is not indicated unless there are extenuating circumstances.

Summary

Infantile cortical hyperostosis is a disease of infancy which is characterized by swellings over bone, and by fever, irritability, a remittent course, and characteristic roentgenographic findings. The disease is much more frequent than is generally appreciated. The course is usually benign, and the treatment is symptomatic.

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Some Epileptic Variants in Childhood

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EPILEPTIC seizure manifestations are not always easily recognizable as such because they may take on more subtle forms than the usual convulsion. The type of seizure which is easiest to recognize is the generalized convulsion (grand mal attack). Staring spells (petit mal, absence or lapse attacks) are more difficult to recognize, and their diagnosis is often missed by untrained observers, or they are disregarded as of no significance. Psychomotor attacks (automatisms) also may be passed off as representing psychologic disturbance. Medically trained individuals would recognize the significance of lapse and of psychomotor attacks, and direct their diagnostic tests and therapeutic endeavors to the brain.

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The usual classification of epilepsy into grand mal, petit mal and psychomotor attacks is a gross oversimplification. Epileptic manifestations are caricatures of the normal functions of the brain and have nearly as extensive a range as the normal activities of the brain. Seizure patterns may be so unusual that even trained observers will have great difficulty in discovering the nature of the disorder. Some of these unusual patterns are described in this discussion.

The Periodic Syndrome

The periodic syndrome is an unusual type of paroxysmal cerebral disorder which has also been termed convulsive equivalent state. This condition, when full-blown, consists of recurrent attacks of abdominal pain, nausea, vomiting, headache and fever. The recognition of this syndrome as cerebral in origin is difficult enough when the picture is complete, but the manifestations may be fragmentary and only one or two of these symptoms may recur in episodic fashion. Abdominal epilepsy is a term which has directed attention to the

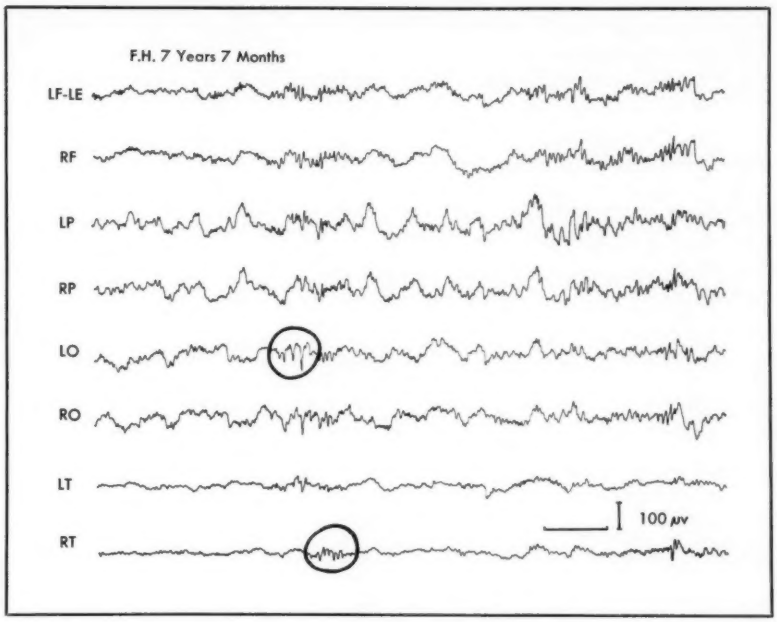

FIGURE 1. The encircled parts of this electro-encephalogram show 6 per second positive spike discharges in the left occipital lead (LO) and 14 per second positive spike discharges in the right temporal region (RT).

cerebral origin of attacks of recurrent abdominal pain. It is equally important to realize that paroxysmal cerebral dysrhythmia may form the basis of episodic vomiting, headache and fever.

Diagnosis is based on consideration of the total picture. The episodes are recurrent and without apparent local cause. The onset is often sudden and the duration short. The grouping together of several manifestations, such as abdominal pain and headache, is suggestive of something other than local abdominal disease. There is no abdominal tenderness in these attacks. The clinical picture is thus different from the ordinary presentation of common intra-abdominal conditions such as ulcer, appendicitis or bowel obstruction. The diagnosis is facilitated if the patient should lose consciousness in an attack, but this occurs infrequently. The appearance of sleep following the other manifestations is very suggestive of the cerebral origin of the symptoms.

A family history of similar disorder may be elicited. The patient may have had convulsions or may have lost consciousness at other times, and these findings would strengthen the suspicion of a cerebral cause for the abdominal or other symptoms.

Physical examination usually reveals nothing abnormal in either the abdomen or the nervous system. If the symptoms are mainly abdominal, roentgenographic examination of the gastrointestinal tract and pyelography will help to rule out the presence of a local lesion. Electro-encephalography is most helpful. It often will show abnormal forms in the course of the attacks and in the intervening periods. If possible, electro-encephalograms should be made both during the attacks and in the intervening periods. The electro-encephalographic abnormality is much more marked during the attacks, and correlation of this disturbance with the clinical symptoms can make the diagnosis certain. The electro-encephalogram made between attacks commonly reveals the pattern of 14 and 6 per second positive spikes in light sleep (figure 1), but paroxysmal slow waves or focal abnormalities sometimes are seen. During an attack, the electro-encephalogram usually shows generalized high voltage, slow wave activity.

Treatment with anticonvulsants may be

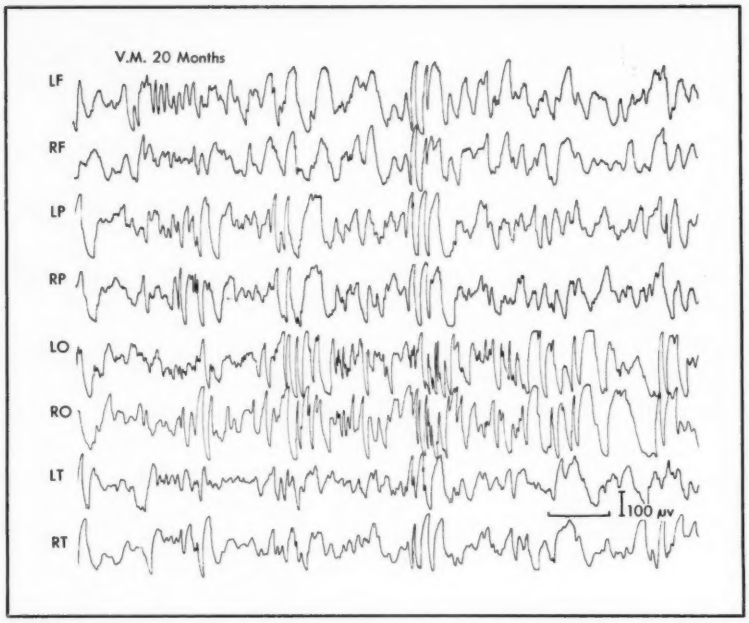

FIGURE 2. This electroencephalogram reveals the continuously abnormal record and high voltage, the slow paroxysmal activity of hypsarhythmia.

helpful both in relieving symptoms and establishing the diagnosis. DILANTIN®, phenobarbital or MEBARAL®, and DIAMOX® are the most useful agents. It may be necessary to use these in combination, for the attacks do not always respond easily to medication. In cases in which the disease at first is manifested only by convulsive equivalent manifestations, loss of consciousness and generalized seizures occasionally develop later.

Massive Spasms

There is a natural tendency to equate the severity of epileptic manifestations with the seriousness of the underlying cerebral disorder. This is evident in the relief parents show when told that their child has petit mal rather than grand mal. This conclusion is often wrong. For example, akinetic attacks in which a patient suddenly falls without convulsive movement usually have a much graver import than generalized convulsions, for the akinetic seizures commonly are associated with severe and diffuse cerebral disease while the generalized grand mal convulsions may reflect merely idiopathic epilepsy in which there is no impairment of cerebral function aside from that of the seizures.

The error in equating the amount of movement in a seizure with the gravity of the condition also becomes evident in consideration of massive spasms. These are attacks which consist of sudden brief abduction and flexion of the upper limbs, flexion or extension of the lower extremities and, often, neck flexion. Such contractions are followed by relaxation, and these spasms may occur in series. They may be associated with other epileptic manifestations, particularly head-nodding attacks. The massive spasms occur in infancy and early childhood, and are a reflection of epileptic discharge in an immature nervous system.

Parents often become accustomed to these spasms and tend to discount them because of their brevity. They may come to the doctor complaining only of their child's slowness in reaching developmental milestones.

These massive spasms may appear superficially to be little more than an excessive tendency to startle, but they indicate severe and diffuse damage to the brain. The almost invariably associated finding of mental retarda-

tion is another reflection of this brain damage, but it represents in part an interference with functioning of the normal brain by the disturbed activity of the regions from which abnormal discharges arise. This effect of the "bad brain" is indicated by the improvement in mentality which occurs when the spasms are controlled by medication.

Electro-encephalography is helpful in the diagnosis of massive spasms. The electro-encephalographic abnormality is usually extreme, and the continuously abnormal pattern of hypsarhythmia is the common finding (figure 2).

The parents should be told the serious significance of these apparently minor attacks, and should be warned of the difficulties usually encountered in therapy. A combination of GEMONIL® and Mebaral has proved to be the most effective means of lessening the frequency of these attacks, but the attacks often cannot be completely suppressed. The massive spasms often disappear by the time the child is two years of age, but seizures of other types may then appear. The mental slowness usually is less marked when the frequency of attacks is decreased, but some degree of retardation is the rule even when the massive spasms stop.

Disorders of Mentality Associated With Epilepsy

Mental dullness as an associated finding in epilepsy is not limited to massive spasms. It may be found together with seizures of any description, although the large majority of epileptic patients have normal mentality. In some cases, the dullness is a reflection of the loss of functional cerebral tissue as a result of the same injury which produced the seizures. Some patients are quite normal intellectually at times, yet at other times may experience remarkable difficulty in their thought processes. This mental slowing often is associated with great irritability and may be evident both subjectively and objectively. Its variable nature is indicative of something other than immutable brain injury as the cause.

The dullness may be a prodrome to generalized seizures or may be an isolated occurrence and persist for hours or days quite separate from other disturbances. When such a variable disturbance in mentality occurs in a patient with epilepsy, attempts should be made to obtain an electro-encephalogram during the periods of mental clouding. The finding of a seriously disturbed record at such times indicates the likelihood that the function of normal cerebral tissue is impaired by the propagated activity of the abnormally discharging neurons. The combination of episodic dullness, irritability and electro-encephalographic abnormality indicates inadequate control of the seizure state and the necessity for further adjustment of therapy.

I am grateful to Dr. Peter Kellaway for the illustrative electro-encephalograms.

The Disturbed Child

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GIVEN all the material, educational and medical benefits of our country, how can we account for the presence of so many unhappy, unpleasant and unproductive adults in our society? Given such basic assets as intelligence and physical well-being, how can we explain the misfits, the psychosomatics, the depressives, the school failures, the unmotivated, the psychotics, the maritally disabled, the individual delinquents and the sexually deviant? It is not sufficiently precise to view these disorders as the compounding of life's multiple pressures. We are in a position to speak with more exactness, and have no need to rely on generalities. The unhappy, the unproductive and the unpleasant adults of our society were the disturbed children of a generation ago—and what is more pertinent, they are the parents of our presently disturbed children.

The general practitioner is in a critical position; it is he who cares for 85 per cent of the children of this country. His detection, treatment and disposition of disturbed children can be a personal, medical, family and social contribution—or they can reflect inadequate understanding and the failure to assume responsibility for his patients in the largest sense. Practitioners for years have struggled with the fact that pediatric practice is a combination of medicating the child and satisfying the family. Psychiatric understanding of the problems of the disturbed child has enlarged this concept to include the intervention and active treatment of many family members. Once again the general practitioner is called on not only

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to diagnose and to treat—he must also educate, as he has had to do with surgery, vaccination and infectious disease.

If a child contracts scarlet fever, is stricken with appendicitis or sustains a severe laceration, parents move quickly to enlist the physician's aid. Parents understand the need for medical care and quickly pay for the privilege of a healthy child. They would as gladly cooperate in the detection of the emotionally disturbed child if ignorance, superstition and poor advice could be overcome. Parents will not remain apathetic about seeking medical care for the emotionally crippled child if they can be educated to the need and potential for preventive and definitive treatment.

A concerned parent often voices recognition of unhappiness and maladjustment in a child, but is spuriously reassured by friends and uninformed relatives that the child is simply different congenitally or will outgrow this "phase." Since the symptoms do not constitute a life-or-death decision, the parents may be lulled into a mood of denial or of procrastination. Such parents often have an unconscious need to perpetuate such a personality distortion in the child, and thus readily concur with the well-intentioned friend.

Unfortunately, the offering of such poor advice is not limited to lay friends; it frequently comes from an equally well-intentioned physician. Because of unfortunate contacts with a few psychiatrists, or because psychiatric intervention may have temporarily inflamed a smoldering situation, or because of his own emotional problems, the practitioner may rationalize by depending on the elixir of time and the salve of sympathetic support. For years psychiatrists were in no position to expect a hearing: We had not yet defined the etiologic factors behind psychiatric entities. The situation is gradually changing. About certain conditions we can be very explicit with regard to etiology and treatment.

Insofar as the medical practitioner is dedicated to the principle of treating illness, he will be interested in acquainting himself with our ability to help parents and children achieve a healthier and more satisfying life. This paper is an attempt to outline some of the areas in which psychiatric understanding can help the general practitioner better treat his disturbed child-patients.

The Socially Disturbed: An Illustrative Case

As a prototype we will briefly discuss a case representing the socially disturbed.

Sam, eight years old, was referred for psychiatric attention because of incorrigible behavior at school, present since kindergarten but completely out of control in the prior three months. He was not only "sassy" and inattentive, but he had begun impulsively hitting things and children on the school grounds and in the classroom. He showed greater concern about breaking objects than about scratching, bruising and hitting his companions. Until the previous year he had had a small group of ruffian friends; at this time even they had deserted him in his defiant isolationism. The mothers in the neighborhood forbade their youngsters to play with him, and his siblings were ashamed to accept him as a brother. For three months he had not smiled, and any attempt to enforce regulations at home was met by severe outbursts of bad temper, including kicking the wall, hitting his mother, retaliatory fecal soiling and impulsive biting of his five year old brother. The younger brother, by contrast, was sweet, lovable and completely tractable.

Medically, Sam's condition was interesting because of encopresis and enuresis. During the taking of the history of the child from his mother, Sam was constantly in motion in the examining room. By the end of 10 minutes Sam had attempted to dismember every object in the room, and was demanding release.

Magically, with the dismissal of his mother, Sam became tractable and even cooperative. It took no psychiatric acumen to realize that Sam's mother represented the yeast in this child's ferment.

The physician who saw the child had confidence in psychiatry and quietly told the mother of the obvious need for specialized help. He was himself so calmly assured and so genuinely motivated in the child's behalf that no referral problem was presented. Psychiatric in-

quiry revealed a child who immediately began testing the limits in the playroom, throwing sand out of the box, crashing cars against the wall and turning on the water in full force.

The woman psychiatrist's initial comment, "There'll be none of that in here," was followed by a look of bewilderment; then the child's question, "You don't want me to mess things up?"

Slowly Sam shook his head and played quietly with the cars. A moment later he tried again; a car crashed against the opposite wall. The woman psychiatrist firmly but kindly said, "Sammy, I want you to have a good time and to talk about feelings—you're not to hurt the room, or me or yourself."

The boy angrily spat, "I hate you," to which the physician responded, "Of course you do, 'cause I won't let you do what you want."

A few moments later "disturbed" child and psychiatrist were building a clay city—the reflection of a single constructive emotional experience. Sam had become convinced for a moment that one woman would limit his behavior but accept his angry words.

What of Sam's mother? As one would guess, she had never been able to limit her son's behavior, except when at long last she became completely torn asunder. Then *her* temper tantrum was even more startling than those of her son—she kicked, screamed, struck out and bit Sam—who could identify in only one direction: that of trying to release his anger as did his mother. During early childhood he had controlled the family, was rarely frustrated and seemed reasonably secure, except for enuresis and encopresis. With the competition of school, and especially since the birth of the younger brother, he had become more demanding and defiant.

The mother was completely overcome, withdrew in limit-setting even more, and began the ritual of saying, "Sammy, why can't you be as good as Brother Joe?" It was not surprising to find that a favored brother had never been restricted in her family. His name? Sam.

The physician-father sheepishly accepted responsibility for his passivity in the vacillating and irrational discipline which this child had received. He was quite aware of choosing attendance at medical meetings or retreat to the study rather than participation in the development and problems of the family.

Comment—This kind of problem needs active and immediate intervention on the part of an interested and sensitized physician. We know many family physicians and pediatricians who have become subtle and expert at taking the kind of history that will reveal what is happening in a family to account for such a child's violent temper or his functional headaches, aching legs, enuresis, fears of going to school, insomnia, vomiting, night terrors—and even year-round asthma, behavioral problems and delinquency. The important thing is *active* and *learned* inquiry into the interpersonal factors behind such a child's family and social disturbance.

Interview Technics

For those who might find it valuable, we briefly outline the salient aspects of collaborative interviewing. No psychiatric evaluation of a child is complete unless both parents are interviewed thoroughly with respect both to the child's problems and to the parents' own growth and development. The abundance with which psychodynamic material develops depends on the patience, subtlety, imagination and dexterity of the examiner as he detects and unravels the clues of the developing psychopathologic process. Experience permits insistence on the presence of interpersonal problems when symptoms are detected; and, as time proceeds, the examiner, to gain the facts necessary for accurate evaluation, feels no hesitancy in commenting on gross deceit or the withholding of information. It must, however, be remembered always that material is interpreted dynamically and in a manner constructive to each person as well as to the total family unit.

The following are the factors investigated with the parents. They constitute a brief outline of the orientation given to psychiatric and pediatric fellows rotating through the child psychiatry service.

1. Present illness: description and temporal correlation with family problems, separations, physical illness, school or social pressures.

History of neurotic traits such as enuresis, nail biting, night terrors.

2. Developmental history: details of nursing, habit training and periods of jealousy, with particular emphasis on parental emotional reactions to the conflicts common to these stages. Inquiry must always be made into the manner of handling biologic questions, particularly in the three to six year period.

3. Discipline patterns: specific examples of limit-setting, handling of frustrations and degree of consistency conveyed by each parent and both parents to the child. Inquiry into each parent's own pattern of discipline as a child.

4. Sleeping, modesty and affection patterns: These entail inquiry into actual arrangement of bedrooms and degree of privacy in sleeping, dressing and bathroom practices. Patterns of physical and verbal affection are obtained in detail.

5. School adjustment: Educational, disciplinary and social problems are elicited with particular evaluation of reading or learning difficulties.

6. Special interests and assets: particularly parents' awareness, participation and reaction to these. Patterns of sharing with friends and siblings.

7. Strength of conscience: evidences of dishonesty, delinquent trends, moral attitudes, religion.

8. Parental attitudes: which parent more kindred to child, expectations at conception and pregnancy, fantasies for child's future.

9. Parental marital adjustment: attitudes during courtship, sexual adjustment, interests, attitudes as spouses and as parents.

10. Parental histories: taken in same orderly manner and detail as that of child.

a. Specific symptoms suggest material to be sought: For instance, in case of school phobia, look for hostile-dependent relationship between child's mother and the mother's mother.

b. Specific conflicts in parental development heighten awareness of present problems: For instance, if mother is overly affectionate to own father, marital adjustment undoubtedly is poor.

It should be pointed out that frequently parents withhold, deny or dissociate significant material, particularly in respect to discipline, seductive affection and sexual adjustment. It also happens that parents will attempt to keep the physician from interviewing the spouse "for fear the stories won't match." At times parents openly lie about serious emotional traumas. Such patterns are a reflection that the parents, too, are ill because of their unfortunate experiences. They cannot be condemned. They must be treated as sympathetically as a child. If parents become hostile toward the physician, a concerned comment regarding the source of this anger may bring further dynamic material. It is important that the interrogator not be deterred by the appearance of rage, disgust, tears or anxiety; these are the reflections of salient emotional factors. In spite of what at first may seem difficult hurdles, the facts must be gathered. Given time and experience, the interested practitioner can obtain a useful and dynamic history.

Consideration of Theory

We should at this point consider theory briefly. For two decades psychiatrists have been saying that the foundations of neurosis, psychosomatic states, certain psychoses and delinquencies are laid down in early childhood, and are in a large measure not constitutional. If detected early and if adequately treated, many of the disorders in question could be alleviated. Many primary emotional disturbances in children stem from the fact that these children are being reared by emotionally disturbed parents who themselves were reared by unstable parents. Neurosis leads to neurosis, and moderately concealed antisocial behavior in parents (delinquency) leads to more frank delinquency in the subsequent generation. This is due to interpersonal exchange and adaptation, not to heredity and the genes.

However, *all* emotional disturbances are *not* caused by disturbed parents; some are a result of disaster. If a mother dies when a child is three years old, for instance, this loss has a profound emotional effect on the developing personality, even in the most normal family. Insofar as parental attitudes and unto-

ward disasters may be harbingers of emotional conflicts in children, they must be detected, and reparations made. Insofar as the emotional disturbances of children are reflections of parental conflict and unhappiness, the entire family deserves and has need of treatment.

Thus has arisen collaborative therapy of child and parents.[1] This technic has become a vital research tool as well, and has offered insights about specific etiologic factors not previously possible.

Basic to the understanding of all emotional illnesses is the understanding of anxiety, that ever-present feeling, common to the emotional disturbances of human beings. It may stand out so strikingly that no one could fail to see it. At other times it is covert, or acted on antisocially, or expressed by means of physical symptoms. What, then, is anxiety? It is akin to fear, but like a mathematical number raised to the fourth or the tenth power, it is beyond and above ordinary fear. It is overwhelming in its permeation, and more frightening because it is so nebulous, until its sources can be realized consciously. Anxiety is ill-defined fear, generated by unconscious conflicts, often not amenable to ordinary reassurance or will power, and usually pushed into greater chronicity by time and increasing environmental pressures.

Probably the greatest sources of anxiety in children today are their guilt, confusion and fear of retaliation related to their expression of anger. If children are to be healthfully reared, parents must expect outbursts of anger to follow frustrations, denials, limit-setting and disappointments. Wise parents do not make the child feel guilty about experiencing anger, but do afford guidance as to how the child may best express the anger; namely, verbally. The parents do not permit the child to destroy property, or to injure others or himself. The healthy parent instills a recognition of guilt about such acts, but at the same time guides the child in the moderate and constructive verbalization of his anger. If the parent is a comfortable person, he can set limits easily and accept the child's verbalized anger without alarm or hostility.

In contrast, the insecure parent responds in one of several ways: (1) He may brutally retaliate: spanking, depriving or rejecting inappropriately, so that the child is frightened about his physical well-being and is rejected emotionally; (2) he may himself be taken by panic, anticipating that the child of five years may indeed murder when he angrily says, "I could kill you"; the child in this instance senses the hostile fantasy of the parent and becomes more anxious as he is pushed in the direction of hostile behavior; (3) the parent may comment, "How can you say such things to your kind, dear mother? I love you more than anyone ever will. Some day, when I'm gone, you'll be sorry." Thus are generated in the child overwhelming guilt and the need to repress expressions of anger.

By these and other parent-child interchanges neurotic anxiety is instilled in the child to form the anlage for emotional illness. A large number of emotionally disturbed children and adults have so repressed their anger that they are not even conscious of it. They are aware only of anxiety or headache or a hundred other symptoms. It may take months in treatment to help the child or adult realize that anger underlies his anxiety, fear and symptoms of neurosis. In his earlier investigative years, Freud believed that sexual conflicts underlay all neurosis. As Freud and other research workers looked more deeply into the unconscious, it became apparent that repressed anger was more the common denominator. To be sure, many sexual conflicts exist in emotional disorders, but this relates to the fact that anger is bound with sexual impulses.

This brings us to consideration of the theory of the presence and importance of the unconscious. In the latter years of the last century one of the greatest discoveries in biologic science was made. Freud perceived and tested the existence of the unconscious; he developed technics for observing and exploring its operations. He proved beyond all doubt that vast reservoirs of the emotional and mental operations that drive us reside in the unconscious, an understanding of which has permitted psychiatry to become a truly scientific specialty. It is now accepted that unconscious mechanisms push and pull us in directions we fre-

quently would prefer to believe consciously maneuvered. This does not mean that nothing can be decided on consciously without interference from the unconscious. It does mean, however, that if painful and conflictual facts have been repressed in the unconscious, rational behavior becomes very difficult.

Of vital importance also in behavioral patterns is the developing conscience. Reflecting and caricaturing the strengths and weaknesses of parental conscience is the mosaic of the child's conscience. A child's conscience is not inherited but is developed, especially during the first six years of life, by means of imitation in great detail of the total behavior of parents. This imitation embraces the conscious and unconscious operations of the parents. To an equal extent, conscience develops from the parents' conscious and unconscious image of the child and from their concepts and hopes for their child. The amalgam of these detailed and specific identifications in the realms of honesty, social behavior, sexual concepts and moral principles forms the child's conscience, basic to the constructive social control of the individual.

Finally, a word about love. In the earlier days in child psychiatry, great emphasis was placed on the need to give the child sufficient love. No one seemed to recognize in those days that the parents were giving as much love to the child as they were capable of mustering. To suggest to such parents that their disturbed children needed more love and affection was redundant. Until such parents could understand their inability to give what should be natural—that is, parental love—they could not act differently. Today we recognize that the parents had parents, too, and that we must help parents if we are to help the child. We have learned that the handling of the child's sexual questionings, his testing of social behavior, his response to discipline, all reflect parental security or uncertainty. With these concepts and technics as a background, let us consider specific disorders.

Acute Emotional Disturbances

Neurotic, psychotic, delinquent or psychosomatic problems may show signs of acute decompensation with the eruption of an acute emergency. The acutely disturbed child needs quick and dynamic evaluation of family psychopathology, with active intervention by a sensitized and confident physician.

Problems to be considered in this discussion of acute disturbances will be limited to: (1) sudden development of severe and incapacitating anxiety and phobic symptoms in reaction to a traumatic event; (2) riotous temper tantrums and allied symptoms so severe as to be dangerous to the patient and people around him; (3) reactions to death and other disturbing incidents; (4) the appearance of massive emotional regression in response to surgical operation. In all these cases the previous personality development decides the "stress-tolerance level" of the child and thus determines how he will react to a serious psychologic trauma, such as death of a parent, divorce, vicious hostile attack by a parent, terrifying cataclysms, birth of siblings or failure at school.

Sudden, overwhelming panic—Let us consider the children in whom overwhelming anxiety abruptly develops to the point of panic. Such children may be screaming, trembling and clinging to the mother, from whom they refuse to be separated. As the attacks progress these children may voice fears of dying, may show extreme motor excitement and the various symptoms of either hyperventilation or hallucinations.

Example 1. A boy of five years was brought for consultation by his father because of the boy's acute hallucination of predatory spiders about to overtake him. Our knowledge that his paranoidally psychotic mother, three days before, had almost choked him to death permitted rapid interpretation of his need to hallucinate symbolically the maternal assault—until such a time as a believing therapist could share with him the actual life-threatening attack which had occurred. Sudden sexual assaults or destructive threats of all kinds may precipitate panic in a child. Such insults are, of course, highly hostile, and the child is terrified by the destructive intent. The child is overwhelmed not only in a physical sense but also by the knowledge that parental "love" in

the instance at hand is destructive. The child's fear and shame at accepting such knowledge precipitate overwhelming anxiety and may necessitate hallucinatory dissociation. Active, interpretive psychotherapy is obviously imperative in such instances, and referral to a competent child psychiatrist is the treatment of choice.

Example 2. In contrast, one might consider a child suffering from a school phobia, another form of an acute anxiety state reflecting morbid fear of separation. Children thus affected may be brought to the practitioner with the complaint of acute attacks of abdominal pain, vomiting, headache, pallor and sweating—and in such states they obviously represent diagnostic problems. In our practice it has become customary to urge that a high index of suspicion be entertained that these symptoms are reflections of anxiety if they: (1) occur before school, only to subside by noon; (2) rarely occur in summer; (3) are seen in families in which parent and child show difficulty functioning away from one another. The factors behind such conditions will be discussed under "separation anxiety," later in this paper. If the symptoms are of recent onset and the truancy marked, immediate psychiatric referral is indicated. In the past, in many of these cases, the condition has been mistaken for rheumatic fever. Rest in bed only made the entire situation worse.

Riotous temper tantrums and allied symptoms—Another type of acutely disturbed child who presents a difficult problem dangerous to both himself and those around him is the one with riotous temper tantrums and allied symptoms. Such children are best handled in the hospital, away from the situation at home. This type of management in itself may eliminate the outbursts and allow the physician to make therapeutic contact with the child. All catastrophic temper tantrums are initiated and fostered unconsciously by the parents, who need treatment if the child is to return home.

We all know today that the setting of reasonable limits is absolutely necessary in the rearing of children, and in many instances in therapy at the onset. The calm, unhostile, consistent adult rapidly has less and less trouble with this, for the patient, removed from the parents, is intensely relieved to have a firm, friendly adult take a guiding hand in control of the riot.

Allen[2] puts it this way: "A skillful therapist has no interest in proving he can *make* a child put away his playthings or clear up the mess he has made during the hour. He will not use the setting of a limit for the exercise of personal power. To do that would be to destroy the meaning of the whole experience, and make it the battle of wills the child may want. Valid limits grow from the situation and belong to it. They do not spring from the personal whims or control of the therapist. Around the natural limits that emerge, a therapist, by clearly defining them, helps the child to face them or to express his feeling about them."

Example 3. Typical of the catastrophic reactions is the condition of an acutely disturbed 17 year old farm boy in whom convulsivelike seizures suddenly developed. They were associated with violent hyperactivity, including attempts to throw himself through a window. His condition at first was thought to be epileptic, and anticonvulsants were prescribed and he was restricted from driving the tractor, his pride and joy. This restriction contributed to deterioration of the situation to the point where commitment of the boy was being demanded by the neighbors. The boy was then hospitalized three weeks. During psychotherapy he came to recognize consciously his feeling of helplessness in the face of his enormous rage toward his semi-invalided and hemiplegic father, who blatantly favored the patient's lazy older brother. The patient was doing practically all the farm work, but his father, possibly partly because of organic deterioration, derogated requests the patient made for machinery and supplies, while lavishing money on the spendthrift elder brother. Before his father's illness the patient had worked closely with his father on the farm, but since that time he could not bring himself directly to express his real feelings of rage. Long treatment after the brief hospitalization helped this patient to face and to deal with his anger more consciously, and no seizures supervened, in spite of the withdrawal of drugs. The boy finally was able,

without a temper tantrum, to tell his father that he would leave the household unless matters were radically changed. By that time the patient could speak with such firm conviction that his father knew the situation was serious and that the boy meant what he said. The parent then complied.

Acute reactions to death and catastrophe—We cannot omit from the subject of the more acute reactions a discussion of the effect of the death of a parent. By the age of two years the child is devoted to his parents. Little children regard death as abandonment, and are terrified and enraged.

Example 4. John, a boy of four years, said, "Mommy is in heaven. She went to Milwaukee last year and came home. Why don't she come home now?" Members of this child's family thought they were supportive when they said, "Mommy was sick, but now she's happy in heaven." This infuriated the child, who immediately assumed she had not been happy at home. In addition, he was driven by the belief that his angry thoughts might have caused her death. This boy needed a chance to grieve openly with the other mourners and to talk of his hate and terror and love. If feelings are smoothed over, all emotion is repressed—the love along with the panic and hate. When the love is repressed along with the hate, the child grows up to be a cold person, unable to realize his potential for loving. If the relatives hesitate to talk about such a catastrophe with the little child, then the physician should do this recurrently and often for some weeks. The practitioner can serve a very useful purpose in these cases by insisting on the child's right and his need to speak of his feelings, to cry and to be angry.

Massive emotional regression—Symptoms of acute neurosis or psychosis, as we have said, may be the results of long hostility and cruelty on the part of adults, exposure to accidents, death or long absence of a loved one, or disturbing experiences, such as introduction to perversion or adult genital exposure. The intensity of the reaction depends on the level of security previously felt with the parents. The inexperienced therapist may, in these catastrophic cases, confuse schizophrenia with massive emotional regression. Typical is the following case.

Example 5. A 12 year old boy underwent craniotomy for removal of a medulloblastoma. The mother had refused the neurosurgeon permission to orient the boy preoperatively. The boy first learned he was to have his head operated on from the barber, who appeared to shave his head at five o'clock in the morning. After the operation, this 12 year old boy regressed to an infantile level, soiling and wetting his clothing, sucking, taking only fluids, whimpering and speaking only a few words of baby talk. This regression was not to be explained by any neurologic or radiologic interference, according to the specialists in these fields. It was immediately obvious that the patient now feared greater physical injury, and especially something castrative. When this fear was discussed in simple terms with him, he manifested his first confidence in the physician. The hostile, destructive mother was forbidden access to the boy, since she had always terrified him. The passive father for once stood his ground and supported us. The psychotherapist encouraged the boy to face his rage and terror at the sudden surgical insult, and correlated these feelings with significant ones from his past. In many such cases intensive work also is done with the parents.

Mention should here be made of an area in which psychologic preparation seems to be preventing acute anxiety and postoperative pain; namely, in instances of amputation. We encounter almost no phantom limbs with pain if four simple matters are discussed with the child (or adult) before the operation. The physician need not be a psychiatrist to manage this well. Often the physician must work very rapidly, since for sound reasons surgical treatment cannot be delayed. The parents give the history, which alerts the physician to the presence or absence of insecurity, physical fears and anxiety, and undue guilt about hostility chronic in the child. We now handle several points in the treatment of all children.

First, we support the surgeon's decision that amputation is necessary, and we encourage the child to face his anger at us about this amputation before and after the operation.

Second, we discuss with the patient his sadness and mourning about losing his old friend —his limb.

Third, we tell him there will be a phantom phenomenon and explain what he will feel.

Fourth, and especially with the older child or adult, we help him verbalize his concern about disposition of the limb. This is a grave concern, particularly in the chronically disturbed patient, and must be discussed freely.

Above all, we do everything we can to help the patients face their anger and sadness. Often much work must be done with parents, surgeons and nurses toward their understanding of and acceptance of the angry, mourning child who has undergone amputation. At first the surgeons felt we only made troublesome patients for them. This attitude has now largely subsided. It is time for these procedures to become part of the medical regimen for patients who must undergo amputation.

The Schizophrenic Child

Some of the most disturbed children are those struggling with schizophrenic thoughts, fears and physical drives or inhibitions. They may show their disturbance either in the form of acute excitement or pitiful withdrawal, colored by hallucinations or delusions, or muted by apathetic desensitization. As soon as the diagnosis is suspected, psychiatric consultation is necessary. The condition of these children, and especially the more autistic ones, often is confused with mental retardation or damage to the brain. Hospitalization may be the only course open, for both proper control and accurate diagnostic observation. Children presumed to be schizophrenic ought to have careful and detailed psychiatric observation, so that those exposed to violent intrafamilial threats may be evaluated for possibilities of treatment.

Some very competent physicians today still maintain that schizophrenia is constitutional and organic, whereas others see it as developing in relation to disturbed and very destructive parents. Certainly, some, at least, of those patients previously considered hopeless now can be treated satisfactorily. This particular field is still open for research, but our observations on the procedure in which we collaboratively and concomitantly treat parents and child incline us more toward the environmental than toward the constitutional view. The most open mind is that which does not, at this stage of research, stoutly maintain an either/or attitude but considers every avenue for exploring the environmental and constitutional factors. For the practitioner this means the referring of such patients *early* to the interested child psychiatrist.

Chronic Emotional Disturbances

Children with chronic emotional disturbances are more usually seen in outpatient clinics, to which they are brought for treatment by the parents or by means of urging from teachers.

Inhibition of learning—One of the most common evidences of emotional disturbance that teachers observe is the inhibition of learning, of greater or lesser degree. Children formerly doing brilliant work may suddenly fail and lose interest. Emotional conflicts with anxiety, inhibitions and depression may account for this. Children thus afflicted are best handled by psychiatrists, but the family physician can clarify emotional problems.

If the learning problem centers largely around reading, a psychiatrist should decide if this is an educational matter or an emotional, conflictual problem. If it is the former, excellent *individual* tutoring five days a week (not after school hours) by a very pleasant, encouraging tutor is the best approach; most parents are unsuitable tutors. If the problem is emotional, the psychiatrist must help the child face his emotional inhibitions. Fear about questioning in biologic and sexual matters often is at the basis of general inhibitions of learning. In these instances, parents have harshly squelched the little child's early guileless questions about sexual matters; subsequently the child is afraid to ask questions about anything for fear of a harsh, rejecting and shaming answer.

Separation anxiety—One of the commonest chronic emotional disorders is separation anxiety, frequently a cause of absence from school and erroneously considered a phobic reaction

to school. A year ago, within three days of each other, two 14 year old girls arrived at the hospital on stretchers. They appeared to be critically ill; the possibility that Addison's disease and other systemic conditions might be present was investigated. The girls were thin, without appetite, very weak, and had been in bed for three months. Investigation showed that the mothers, unhappy in their marriages, had been overly concerned about any aches or colds in the children, and had fostered regression and hostilely frustrated growth in many ways. They were attempting to hold these girls close, to buttress their own insecurity. The results were very sick children, on whose continuing invalidism the mothers were parasitically dependent. In a few days of collaborative treatment, each mother and daughter were coming to our offices. Active, intensive early treatment broke up the destructive physiologic and school problems, and permitted a return to school with a foregoing of the immature gratification of their neurotic tie to the mother.

Boys become involved in separation anxiety exactly as do girls, and many times the fathers may be important etiologic factors in the hostile-dependent tie. Whoever is of greater importance must be treated with the child. Twelve years ago such problems were not understood; these children became invalids or at best inadequate and neurasthenic. Separation anxiety, with all its ramifications, is the core-conflict of many adult neuroses. Papers published elsewhere describe the details of actual psychotherapy.[3,4] Any interested practitioner can apply the technics as described in these papers.

Psychosomatic illness—Although not so obviously disturbed emotionally as are members of the preceding groups, the psychosomatically ill are afflicted with a degree of disturbance which must not be overlooked. A case may illustrate.

Example 6. Rickie was seen at the age of two years, because of chronic constipation. Toilet training had been begun when he was 18 months old and success had been obtained for a month. Then the child began to refuse to cooperate with the routine, and constipation started. The pediatrician suggested that the mother quiet her fears and allow the child to decide about toilet habits. One and a half years later the child was admitted to the hospital with obstipation and fecal impaction. Megacolon was demonstrated by roentgenograms, and there was a stricture at the rectosigmoid. Surgical intervention was deferred because of the *surgeon's* belief that psychiatric intervention would be more appropriate.

It became quickly apparent that this child's mother expected and admired automation, that the pleasure of maturing and of play of any kind was foreign to her psyche and that the child's independence had indeed met a testing ground in the matter of bowel performance. This child was disturbed in all testing situations; on the part of the mother there were constant nagging, whining and demands. On the other hand, with the play therapist, once limits had been set, this child was lovable, imaginative and spontaneous, without undue demands. The mother had indeed relaxed her concern about toilet habits but she had almost totally rejected the child, in play, by vacillating limits and by absolutely no support in the child's attempts to overcome obstipation. Even when she learned of the child's successful evacuations of the bowel in the play situation she "neglected" to provide ready accommodations for such an action for the child at home. Wise was the surgeon who saw this anxious child whose physiology also was disturbed.

It is impossible to discuss the mechanisms present in all, but patients with the following symptoms should be studied with a view to defining the etiologic importance of emotional factors: enuresis, tics, vomiting, constipation, soiling, nail biting, year-round asthma, refusal to eat, phobias, unexplained paralysis of an arm or leg, blindness, episodes of fainting, obsessive fears and thoughts, the need to do things by rituals, inhibition in activities, negligible interest span, inability to make and hold friends, continuous crying, sensitivity and sadness, terror of leaving the mother, violent bursts of hatred, bizarre pains and disorders of the skin.

The Delinquent Child

Still another category of disturbed children compels our attention; namely, the delinquent

child who becomes the psychopath at a later age. In contrast to the overly guilty neurotic person, in these cases we see too little guilt. Two large categories of antisocial behavior can be defined: the individual delinquent and the gang delinquent.

The individual delinquent—First, let us consider the lone delinquent. Mystery enveloped causation here until 15 years ago, when several of us began to treat these children collaboratively.[5,6] Startling facts emerged, and we never fail to find similar facts in every case of delinquency. The facts are that the parents are unconsciously fostering and condoning the delinquent behavior. The parents of delinquent children unconsciously gain satisfaction from the specific antisocial behavior of the children. Interns and residents, early in training, are shocked and skeptical about such an assertion. When, however, they interview parents in the manner we outline, they too emerge in possession of such disturbing facts.

Always we find that impulses toward behavior similar to that in the child are present in these parents: These impulses are unconscious, poorly inhibited and close to breaking through into consciousness. These impulses do break out, sadly enough, by means of fostering such behavior in a child.

Consciously, most of these parents are deeply concerned at the child's misguided behavior, and have no idea that they are actually promoting it. These parents foster conscience defects in their children. There is rarely generalized weakness of the conscience, but rather, a lack of conscience in certain of the circumscribed areas of behavior. The child's antisocial behavior is correlated with the specific area of weakness in the parents' conscience.

The reader will immediately ask two questions: "How do you explain the fact that only one child in a family of three or five children may be delinquent?" and "If the parents do initiate and foster such a defect in conscience, just how do they do it?"

Suffice it to say that each child in a family has a particular emotional meaning to the parents and therefore is subject to highly specific identification and fantasies. For example, a mother with a lying father sooner or later chooses one son to identify with her disliked father, and unwittingly assumes she will never be able to train that boy to tell the truth. She is paralyzed in patiently training him as she trains the other children about truth. Conscience defects are molded in a child in scores of ways of which the following are examples.

1. The parent is vacillating, and may say one thing, only to undo it in the next breath. A mother says it is wrong to steal, but when her child is caught, she covers up for the child. A 14 year old boy brought to us because of extortion said that when his father accused him, quite correctly, of stealing from his wallet, the mother intervened with the statement that she had spent the money. She was deriving unconscious gratification from her son's stealing.

2. Parents will say, "You may not play with fires," but undo the prohibition by adding, "But if you must get it out of your system, we can set fire to papers in the sink." It should be clear that no one has to get fire-setting out of his system.

3. Issues are so befogged by parents that the child can only be confused. Told on the one hand to be honest, the child detects dishonesties in the parents. The parent, with a sly smile, may remark that the grocer short-changed himself, yet overlook a healthy challenge from the child to tell the grocer. Instead of making clear that dishonesty under all conditions is wrong, parents act as if there can be exceptions.

The same double standard recently was clearly shown in newspaper accounts of the father of an adolescent who, with a group, killed an old man. The father of one of these adolescents said, "I can see murder for money; but just to murder, I can't understand that in my boy."

4. Interesting, smiling responses are seen on the parents' faces as a child recounts forbidden behavior at school. Such glances portray parental vicarious gratification obtained by the child's misbehavior. These parents later may spank the child; however, punishment after ardent listening serves as no prohibition. The child will repeat what he feels gives the parent gratification.

5. Once the child notes parental deception, he begins to blackmail the parent. For instance, a mother may write an illicit excuse to the school to cover an absence. It is not surprising that the child will demand another excuse whenever it seems opportune. The problem of delinquency becomes compounded by temper tantrums which the child soon learns are effective in overwhelming a vacillating, corrupt parent.

In a normal home, consistent, never-faltering training goes on daily with regard to truth, possessions and person. The normal parent knows emphatically that with training her children will develop consciences like her own, in which there is no alternative about antisocial impulses. The training is consistent, so that little thefts and untruths are immediately curtailed. The mother or father who permits minor thefts with the idea that the child "will outgrow it" is only fostering further trouble. The normal parent knows that constant training is necessary, but it never occurs to her that her child will ever reach a delinquency court or a reform school. Such fantasies are expressions of what the parents think of the child; they are common among parents of delinquent children.

Among the sexual delinquents, too, parents unconsciously foster the particular form of misbehavior.[7,8] Children behave sexually in accordance with the parents' conscious and unconscious image for the child. Reflective of problems which may develop is the following.

Example 7. A depressed 42 year old woman came to consultation complaining of the sadistic promiscuity of her 20 year old son. Since his adolescence, the mother had intently listened to the minutest details of his intimacies with girls. She was most unhappy with her passive and submissive husband. The sources of her ambivalent seductiveness with her son were easily adduced. Her own father had been a Don Juan. From her early adolescence he had come to her bedroom nightly to fondle her, and he had even made attempts to enter her bed. At the first such instance, this patient sought protection from her mother. The mother did not dare to reproach the father "lest he kill her." From the father, to the patient, to her son, sanctions of the forbidden are evident in three generations. The son, refusing treatment, will provide still another generation of pathologic involvement.

The gang delinquent—What distinguishes the individual delinquency just discussed from that great mass of sociologic or gang delinquency? In the individual delinquent from "acceptable" families there develops a conscience defect *unconsciously* fostered by the parents. There is a conscience defect in sociologic delinquencies by our standards, but it is *conscious;* the parents are quite consciously in accord with the child; there is nothing unconscious about it. It is their world against our world. Their culture avows it is all right to steal or to betray the other world. Trickery, vandalism or extortion against the other group is consciously condoned. In the instance of sexual misconduct the parents' own sexual aberrations are overtly revealed to the children without guilt, and later the grown children behave accordingly. These children are not being driven by the parents' unconscious wishes, but rather, by a gregarious need for acceptance.

It is of interest that in areas of delinquency one may find many well-behaved and stable children because they are being reared in families in which the parents are truly normal, setting limits effectively, guiding their children consistently and affectionately, uninfluenced by the culture of the area. One of our foremost educators was reared in a slum area in which delinquency was rampant. Six of his early friends had been sent to the gas chamber. The educator, however, had been reared by poor but affectionate, consistent parents who emphatically set limits about all behavior that tended to deviate. His family did not accept the mores and standards of the underprivileged of the area in which they lived; thus the child did not become delinquent.

Identification of the type of delinquent must rest with the psychiatrist, the sociologist, social worker and psychologist. A thorough study must involve the parents as deeply as the delinquent. Treatment of either kind is a monumental challenge. The individual delinquent cannot be treated, if the child remains in the

home, unless the parents also are treated intensively. Such treatment must be done by specialists, and it is as difficult as any treatment that ever confronts the psychiatrist. If the parents are not motivated or cannot be treated, then treatment of the child must be carried out in a hospital over a very long period. Treatment of the sociologic delinquent is best conducted through sociologists, community leaders and those working in the antisocial areas. Psychiatric treatment is illogical and ineffective for members of these sociologic antisocial groups. This is a formidable task requiring improved living facilities and new leadership.

Summary

We have briefly reviewed some of the problems presented by disturbed children. Their presence is everywhere, and our plea to the general practitioner is that of sensitization to their ubiquity. The socially disturbed, the acutely anxious and the delinquent need immediate psychiatric referral. The schizophrenically disturbed need careful psychiatric observation, preferably in a hospital.

With regard to the chronically emotionally disturbed, much depends on the time available to the practitioner for inquiry into intrafamilial and intrapsychic conflicts. As practitioners gain confidence in the importance of emotional factors, they will feel more assured about their own inquiry, and psychiatric referrals will be made without apology. Children rarely show embarrassment at seeing a psychiatrist, but the physician's apologetic referral may heighten the parents' shame to the point of great and unnecessary distress. With our present emphasis on total medical care, inquiry into emotional problems must become an integral part of a medical evaluation.

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Books Received

Books received are acknowledged, and, as space permits, those of principal interest to our readers are reviewed more extensively. Reviews appear in this issue starting on page A-104; additional listings are on pages 210, 298 and A-112.

Physical Diagnosis; Principles and Methods. By Simon S. Leopold, M.D., Professor of Clinical Medicine, School of Medicine and Graduate School of Medicine, University of Pennsylvania, Philadelphia. Ed. 2. 537 pages with 379 illustrations and 25 color plates. 1957, W. B. Saunders Company, Philadelphia and London. $9.00.

Occupational Diseases of the Skin. By Louis Schwartz, M.D., retired Medical Director, United States Public Health Service, Louis Tulipan, M.D., Emeritus Clinical Professor of Dermatology, New York University-Bellevue Post-Graduate Medical School, New York City, and Donald J. Birmingham, M.D., Medical Director, United States Public Health Service, Washington, D.C. Ed. 3. 981 pages with 189 illustrations and two plates in color. 1957, Lea & Febiger, Philadelphia. $18.00.

Magnetic Removal of Foreign Bodies. The use of the Alnico magnet in the recovery of foreign bodies from the air passages, the esophagus, stomach and duodenum. By Murdock Equen, M.D., Founder and Chief of Staff, Ponce de Leon Infirmary, Atlanta. 94 pages with 119 figures. 1957, Charles C Thomas, Springfield, Illinois. $4.50.

Obesity; Its Cause, Classification and Care. By E. Philip Gelvin, M.D., Associate in Medicine, and Thomas H. McGavack, M.D., Professor of Clinical Medicine, New York Medical College, New York City. 146 pages. 1957, Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. $3.50.

Signs and Symptoms. Applied pathologic physiology and clinical interpretation. Edited by Cyril Mitchell MacBryde, M.D., Associate Professor of Clinical Medicine, Washington University School of Medicine, St. Louis. Ed. 3. 973 pages with 191 illustrations and six color plates. 1957, J. B. Lippincott Company, Philadelphia and Montreal. $12.00.

Teeth in the Growing Face

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TEETH contribute much to the growing face; they add substantially to its height, to its beauty, and to its symmetry. In addition to this, in a functional capacity, teeth act as grinding mills. In this role they prepare fuel for the physiologic engines of the body.

Repair of carious teeth is a dental problem. Growth of the face, eruption of teeth, and growth of alveolar bone are as much dental as medical problems, because the growing face is an integral part of a growing child.

I shall approach this theme of teeth in the growing face from two points of view. First, I shall show how important teeth are to facial growth and maturation by discussing the influence erupting teeth and their supporting alveolar bone have on the growing face. The second point of view will illustrate the change in the normal growth and eruption pattern of the teeth and their supporting alveolar bone which is brought about by such impacts as supernumerary teeth, premature loss of teeth and thumb sucking.

Tooth Eruption and Facial Growth

Teeth and the alveolar bone about their roots add significantly to vertical and, in a lesser degree, to horizontal facial growth gradients. Alveolar bone is a special-purpose bone. This bone is similar architecturally to basal bone which makes up the maxilla and mandible, the facial bones present at birth. Since the purpose of the alveolar bone is specifically to support the teeth, it does not make its first appearance in the oral cavity until the deciduous teeth begin to erupt.

The deciduous tooth crypts are in basal bone before these teeth erupt. There are a like number of crypts in the mandible and maxilla. In each jaw, 10 are available for deciduous teeth and, most generally, 16 for the permanent teeth. Alveolar bone is added to the den-

tal ridges of the maxillary and mandibular basal bones when the deciduous teeth begin to erupt from their crypts. Thus alveolar bone becomes a continuation of basal bone. It grows to one level concurrently with eruption of the deciduous teeth, and to a higher level with the permanent teeth.

A portion of alveolar bone is lost when deciduous teeth are shed. That portion of alveolar bone is added to the dental ridges again with the eruption of succedaneous teeth. These are 20 permanent teeth which succeed the deciduous teeth. Additional jaw length as well as additional alveolar bone is needed to accommodate the 12 permanent molar teeth, three of which erupt on each side of each jaw. This space, in the maxilla and mandible alike, is provided by a dual process which is not alike in both jaws.

Growth in the maxilla occurs in the diagonal sutures which delineate the upper part of the face from the cranium. This growth is expressed as a downward and forward migration of the upper part of the face. Concurrently with sutural growth, bone growth is taking place in the maxillary tuberosities. This growth provides space for each of the three molar teeth by increasing the maxillary tuberosities and by increasing the maxillary length. These teeth make their appearance in the mouth about the ages of 6, 12 and 18 years, respectively.

Alveolar bone growth proceeds concurrently with the eruption of each molar tooth; thus, each molar tooth adds materially to the vertical growth of the face.

The dual growth process in the maxilla is synchronous with a dual growth process in the mandible. Although growth in the mandible itself, not considering alveolar bone, is different, the growth resultants in the lower jaws complement each other.

Space in the mandible for the three molar teeth is provided in the following manner: bone growth from cartilage proliferation in the mandibular condyles, and growth and remodeling of the ascending ramus and body of the mandible. This remodeling is by resorption of bone on the anterior border of the ascending ramus and by deposition of bone on its posterior border. Thus mandibular body and ramus alike become longer. Growth of the mandible in the vertical and horizontal axes is co-ordinated with eruption of teeth and with alveolar growth. Horizontal and vertical growth of the face may be summarized as being a composite of bone growth in the sutures of the upper part of the face, bone growth in the mandibular condyles, and alveolar bone growth in both jaws.

There are known instances of partial or total anadontia (absence of teeth) in which the face seems to mature to normal proportions. In such cases, closer study of the face reveals it has grown well horizontally. One would expect this because sutural and condylar bone growth is not interrupted or halted by the absence of alveolar bone growth. The growth deficit in partial or complete anadontia is in the vertical axis of the face; the deficit is in facial height. This is the growth direction dictated by tooth eruption and alveolar growth.

Alveolar bone remains so long as teeth are present. When they are lost, it diminishes gradually; ultimately, it is completely spent. Thus it is a superstructure, an outgrowth of maxillary and mandibular basal bone, for the sole purpose of maintaining the teeth and aiding in the vertical growth of the face.

In addition to the part teeth play in facial growth, they and their supporting bony structures also aid in maintaining the contour of the musculature and other soft tissues of the face. Here they act as a bony scaffolding for the soft tissue draperies which make up the face. These soft tissue draperies, particularly the lips and cheeks, rely on the teeth and their alveolar bone for contour, symmetry and beauty. If the upper or lower, or both sets of teeth protrude, the soft tissues which drape these teeth appear bulky. When this occurs, the lips are no longer esthetically pleasing to the eye.

To illustrate inharmonious facial extremes, we only need to remind ourselves of two well-known comic characters, Andy Gump and Popeye. Andy Gump's facial disproportions are diametrically opposed to Popeye's. The former has an excessive maxilla and no chin,

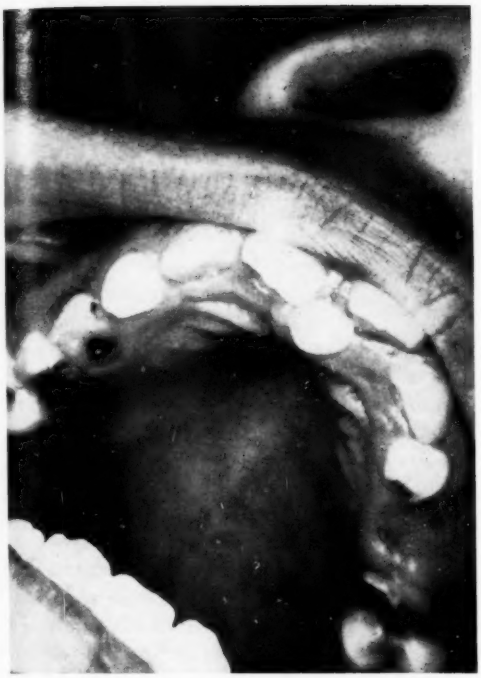

FIGURE 1. Supernumerary teeth between the upper incisor teeth.

while the latter has a large mandible and chin and a small maxilla. In either case, lack of harmony in the bony scaffolding leads to disproportional distribution of soft tissue draperies which is esthetically displeasing.

These comic characters have human prototypes. Fortunately, they are not very common. However, when these tendencies are present, they can be recognized in a relatively young child. Frequently, they can be intercepted orthodontically at an early age. A young child receiving this attention may be spared the psychologic trauma which such deformities inflict on his personality.

Having illustrated the part teeth and alveolar bone take in normal facial development, I shall discuss the factors which impede normal dental and facial development.

Supernumerary Teeth

Supernumerary teeth, extra teeth to the normal complement, may be likened to parasites. As their name implies, they usurp space in the jaws provided for other teeth or, by virtue of their position, prevent the normal eruption of teeth in their immediate area.

FIGURE 2a. Supernumerary tooth causing eruption disturbance of permanent tooth.

FIGURE 2b. Supernumerary tooth causing excessive rotation of permanent tooth.

FIGURE 2c. Supernumerary tooth causing larger-than-normal arch length.

Supernumerary teeth are generally peg shaped or screw-driver shaped, or they may be morphologically similar to the teeth from whose embryonic buds they developed. These teeth may be found in the deciduous as well as the permanent dentition, in any area of either dental arch. Although supernumerary teeth are to be found in both dental arches, they have the greatest predilection for the maxillary incisor area (figure 1).

Failure to recognize these teeth when they appear in the dental arch or to identify them in the roentgenogram when they have not erupted frequently results in eruption disturbances of either deciduous or permanent teeth adjacent to them. These disturbances usually take the form of excessive rotation of the adjacent teeth, of eruption failure of these teeth, or of development of a larger-than-normal arch to accommodate these additional teeth (figure 2a, b and c). Early removal of supernumerary teeth, as soon as they are detected either visually or roentgenographically, is indicated as a prophylactic measure to intercept a serious malocclusion development.

Premature Loss of Teeth

Deciduous and permanent teeth alike may be prematurely lost. The premature loss of deciduous teeth yields a set of conditions different from those caused by a similar loss in the permanent dentition; for this reason, consideration will be given first to an early loss of deciduous teeth.

It was stated elsewhere in this paper that the 20 deciduous teeth are replaced by an equal number of permanent teeth. From this one might assume that the space in the dental arch corresponds in size for this like number of teeth in the deciduous and permanent dentitions. Precocious loss of one or more deciduous teeth creates a situation which permits the remaining deciduous teeth to migrate into the edentulous spaces. This migration reduces the arch length provided by the deciduous teeth for their permanent successors. When the arch length is reduced, some of the vertical growth increment which contributes to the vertical height of the face is also lost.

Following a premature loss of deciduous teeth, there is a usurpation of space which is needed for the permanent tooth or teeth. This precludes its or their eruption into a normal line of occlusion. Thus these permanent teeth may erupt buccally or lingually or they may become impacted by the other teeth (figure 3a, b and c). It is not uncommon to see, as a result of premature loss of deciduous teeth, upper or lower second premolar teeth, or both, erupting into the palate or into the floor of the mouth. High-erupting permanent canine teeth create another form of malocclusion which is frequently due to a premature loss of deciduous teeth (figure 3d).

Another significant period in the eruption chronology of the teeth in the growing face appears at about the sixth year. The first permanent molar teeth erupt at this time, and their appearance initiates the beginning of the permanent dentition. These teeth erupt posterior to the second deciduous molar teeth. These teeth are frequently mistaken for deciduous teeth, and are prematurely extracted in a highly caries-susceptible mouth. When this occurs, a chain reaction follows which results in a severe malocclusion. This malocclusion is identified by the spacing of teeth and the loss of alveolar height in the area of tooth loss.

Permanent incisor teeth which begin to erupt at about the age of seven years are in constant jeopardy. These teeth are frequently broken or lost in bicycle accidents. The loss of these teeth either during the accident, or subsequently by pulp degeneration and abscess, poses a serious problem. The remaining permanent teeth which are to erupt later will drift into the edentulous area if the space is not adequately maintained. Should these teeth drift, a malocclusion will develop in which facial and dental symmetry is lost. Thus it becomes extremely important that accidental loss of anterior teeth be reduced as much as possible. If these teeth must be lost, provisions should be made to maintain the space until the remaining permanent teeth have erupted. The prematurely lost tooth or teeth can then be permanently replaced.

At this point it might be well to ask, "How can the physician help in what appears to be

FIGURE 3a. Buccal eruption of lower second bicuspid tooth.

FIGURE 3b. Lingual eruption of upper second bicuspid tooth.

FIGURE 3c. Lingually impacted upper canine tooth.

FIGURE 3d. High-erupting upper canine tooth.

strictly a dental problem?" In most instances the premature loss of deciduous teeth is caused by dental caries. It is an accepted fact that dental caries can be dietarily controlled by a reduction of refined sugar intake. In the area of diet, the physician's advice is heeded more closely than is that of the dentist. Then, too, it must be realized that a dentist, as a rule, does not see the child much before the age of three. By this time dietary habits are well established; many teeth are hopelessly decayed by the third year if the child leans toward a refined sugar diet.

Control of dental caries has a broad scope; it is as much a medical as it is a dental problem. Failure of parents, physician or dentist to approach the caries problem realistically while the child is very young usually means disaster to the deciduous and permanent teeth alike. Since facial growth relies so much on tooth eruption and alveolar growth, every precaution should be taken to insure their normal occurrence. Dental longevity is a team project, the physician, the dentist, the parents and the child sharing equal responsibilities.

A word should be included here about the physician's responsibilities in accidents in which teeth have been damaged. The nature of the accident is generally such that the parents' first thought is the physician. A cursory examination will reveal loose teeth or damage of teeth. The early protection of an exposed pulp may mean the difference between indefi-

nite retention or premature loss of an accidentally damaged tooth. Thus again, as with dental caries, the physician can play an important part in preservation and maintenance of a child's health by recognizing the extent and the nature of the dental damage and by insisting on immediate dental aid when it is needed.

Thumb Sucking

The stigma which various sucking habits may leave on the teeth in the growing face is still an open chapter. A question asked more often of a physician than of a dentist by mothers of infants and children is, "Can thumb sucking cause protruding teeth?" The question, or perhaps the answer to it, comes to the dentist at a much later time than it does to the physician.

There are three schools of thought pertaining to this question. There are those who feel that the perverse muscular forces which accompany this habit cause the upper teeth to protrude and the lower teeth to retrude slightly. In the second group are those who contend that a similar malocclusion may be found in children who have never sucked their thumb. This is undeniably true. There are delineating factors an orthodontist trained in facial growth and development recognizes, which distinguish a malocclusion stemming from perverse sucking habits from one of genetic origin. The third school of thought contends that thumb-finger sucking or tongue sucking habits play no etiologic role in the development of malocclusion.

Admittedly, such divergent opinions mean one thing: There are fewer facts than hypotheses. Looking objectively at the bulk of information on this subject, one is compelled to admit that most of our present knowledge is inferential. It is based on observation and speculation rather than on a logical analysis of forces inherent to this habit. For this reason, I have chosen to analyze, first, the forces which operate on maxilla and mandible when a child sucks his thumb, and, second, to appraise their effects.

Assuming that an infant begins to suck his thumb shortly after birth, forces from this habit are imposed on the gum pads and subjacent maxillary and mandibular basal bones in a horizontal and vertical plane in somewhat the following manner (figure 4): The distal part of the thumb phalanx is thrust rhythmically by the tongue against the maxillary gum pad. The direction of this force onto the gum pad and the part of the maxilla which underlies it has a forward displacing effect on this part of the bone.

A portion of the force from sucking is brought to act on the proximal part of the flexed thumb, simultaneously with the force on the maxilla. This part of the thumb lies diagonally forward. Thus, it rests across the labial surface of the mandible which corresponds in width to the lingual surface of the maxilla. The sucking force which acts on the proximal part of the thumb moves the mandibular teeth posteriorly and the maxillary teeth anteriorly.

To summarize, the forces from thumb sucking are so directed that they can cause (1) an advancement of that part of the maxilla and alveolar process in which are imbedded the upper anterior teeth, and (2) a retrusion of mandibular incisor teeth and alveolar bone.

In addition to these consequences, which are the product of a combined action of the mandibular elevator muscles and of the intrinsic muscles of the tongue on the thumb, further impact may come to the teeth and to the alveolar bone from still another source, namely, the buccinator mechanism.

The muscles of mastication are for the most part the mandibular elevators. They shorten when a sucking or a sucking and swallowing act is carried to completion. Simultaneously with this shortening, the buccinator mechanism from the facial group is also contracting.

This muscular band which surrounds the teeth on their cheek and lip surfaces is anatomically divided into three parts. There are two buccinator muscles in each cheek whose fibers run posteroanteriorly from a vertical raphe (pterygomandibular) found behind the last molar teeth to the corner of the mouth. This forms the center of the buccinator mechanism, its first part. At the corner of the mouth, the upper fibers go to form the lower lip, and

the lower fibers, the upper lip. Jointly they form the orbicularis oris muscle, which is the anterior part of the buccinator mechanism, its second part. The posterior extensions of the two buccinator muscles form the superior pharyngeal constrictor muscle, the third part.

When this horizontal muscular chain contracts, as in swallowing or sucking, it has a tendency to narrow both dental arches. Thus, when the teeth are parted, as in thumb sucking, the horizontal force directed against the upper teeth is greater than it is against the lower teeth, because the upper muscle fibers are more taut than the lower. This narrows the upper dental arch more than it does the lower arch in a transverse plane. This causes a cross-bite of the molar teeth.

The mechanics and the possible effects of the forces inherent in thumb sucking have been appraised. Does this mean that every child who sucks his thumb is going to have protruding teeth and teeth in cross-bite? The answer is an unequivocal "No." It is generally believed that early interception of the habit prevents lasting dental-facial deformity. By early interception is meant some time before the deciduous teeth are lost. If the habit persists into the eruption period of the permanent dentition, a dental deformity usually ensues. This deformity is proportional to the time and vigorousness of the indulgence.

Were I to take the liberty to express a clinical opinion on when the habit should be broken, I would say as soon as it is first noticed. Thumb sucking, like other conditioned reflexes, becomes progressively more difficult to deter as it becomes firmly ingrained with time and indulgence.

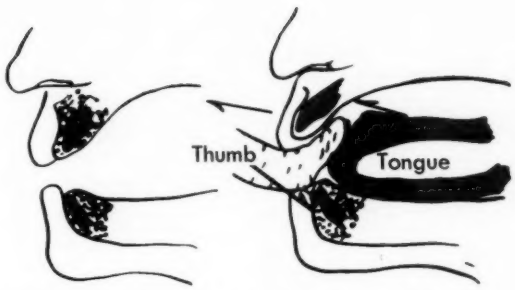

FIGURE 4. Arrows indicate how the forces from thumb sucking are expressed on upper and lower anterior teeth.

Summary

Teeth and their supporting structures play a very dominant part in the growing face. Their guardianship is a team project. A physician is the more important part of this team during the formation and eruption of the deciduous teeth, and during the development of many of the permanent teeth. He, most generally, does not begin to share his responsibilities with the dentist until all of the deciduous teeth have erupted (three years) and some of the permanent crowns have developed. Physician and dentist share dental responsibilities from the child's third to his eighth birthday. From then on, the dental problems are taken over by the dentist. It may sagely be said that the physician is the child's medical-dental guardian for at least the first half of the "teeth in the growing face" period.

Guides for Clinical Diagnosis of Some Infectious Diseases

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TODAY the opportunities of the medical student to acquire practical knowledge of the contagious diseases are greatly limited. Therefore, it is not strange that when he enters the practice of medicine he is likely to commit errors in diagnosis which would have been considered unpardonable 10 or 15 years ago.

Some of the so-called common contagious diseases are rarely encountered now either in small communities or in large cities. This very fact may lead to the belief that certain diseases have been banished. Therefore, they are given no thought when a differential diagnosis is being made. For the most part, it is the bacterial infections which have been subdued, but they have not been eliminated. An outstanding example of what has occurred is the decrease in the incidence of typhoid fever, diphtheria and scarlet fever. Also, tetanus and whooping cough may be included.

In respect to the virus diseases, with at least one exception, their incidence seems to have been altered very little if at all. Measles, chickenpox and mumps appear to occur with the same frequency as in bygone years, and the incidence of German measles (rubella) is much the same as in the past. This situation for these common virus diseases is likely to continue until some reliable methods for active immunization are established. The mumps vaccine now available is said to afford protection for from six months to one year. But any demand for its use ordinarily is limited to male adults. Before puberty, mumps complications seldom occur; therefore, there is little to gain by attempting to ward off this infection during childhood. The one virus disease against which absolute protection can be afforded is smallpox. It nevertheless is interesting to note that 1954 was the first year in the history of this country that no case of smallpox was reported.

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For approximately 30 years I held clinics for medical students at the Chicago Isolation (smallpox) Hospital. There has been no smallpox in Illinois since 1947, according to the records of the Illinois State Department of Health. The smallpox hospital in Chicago was closed at the end of 1949.

Smallpox

How can a physician be expected to make a correct diagnosis of smallpox if he has never seen a case of this disease? In most instances, there should be little difficulty in spite of that fact because the decision generally lies between smallpox and chickenpox. Under such circumstances, the only real requirement for a correct diagnosis is to determine whether or not the patient has chickenpox. But one may ask just what is the difference between the two eruptions.

In any case of eruptive disease, the first thing to note is the location of the lesions. Smallpox eruptions have been classed as centrifugal; the lesions predominate on the extremities. The head, hands and feet may be thickly studded with the lesions, which diminish as they appear toward and on the trunk. If there are any areas of the body which have been subjected to irritation before the onset of the disease, they generally are the sites of confluent patches of lesions. In cases of smallpox, the lesions are approximately in the same stage of development in a given area.

Chickenpox

This disease is characterized by a centripetal eruption, which means the lesions predominate on the trunk regardless of how numerous they may be elsewhere. But it is not extremely rare to find chickenpox lesions on the palms of the hands and soles of the feet, areas which are often extensively involved in smallpox. And in either disease examination of the mucous membranes may disclose an eruption. Since chickenpox lesions appear in crops, they are in different stages of development side by side. Moreover, they are one-cell superficial lesions which rupture easily.

After one has made the differential diagnosis on the basis of the distribution and character of the eruption, a thorough examination should be conducted to determine if the patient has a typical vaccination scar. In this connection it is well to remember that every vaccination is not performed on the arm. This statement does not pertain solely to the female sex, although in most instances in which the vaccination has been on the calf of the leg, the thigh or shoulder, the vaccinated persons have been females. A county health officer in California has reported that he has all smallpox vaccinations performed on the back. The reason given for this choice is that the site of vaccination cannot be reached by the patient's hands, and, consequently, secondary infection is not likely to occur. The presence of a typical vaccination scar should cast great doubt on a diagnosis of smallpox. But it is not a good policy to determine the vaccinal status in a case of suspected smallpox before establishing a clinical diagnosis based on the distribution and character of the lesions. Otherwise, if the physician finds a good vaccination scar, he may announce that the patient has typical chickenpox. But when the suspected smallpox patient has no vaccination scar, the same physician may be bewildered and unable to decide whether the eruption is smallpox or chickenpox.

There is nothing more important in the diagnosis of skin disorders than close observation. In the acute infectious diseases which are characterized by an eruption, a visual diagnosis is often invaluable. If the disease is contagious, immediate steps can be taken to prevent its spread. This applies particularly to smallpox because persons who have been in contact with the patient must be sought and vaccinated at once. Moreover, if the patient has been a traveler, he may have exposed susceptible persons throughout an extensive area.

In the foregoing discussion, chickenpox has been emphasized because it is likely to be confused with smallpox. Occasionally, however, it is mistaken for Kaposi's varicelliform eruption. The latter is due to the virus of herpes simplex, and may recur as in the case of herpes labialis. The lesions have the typical appearance of chickenpox, but there is a characteristic feature. The eruption is present only on

FIGURE 1. Illustration of unilateral distribution of lesions in herpes zoster. Although serious injury to the eye was feared, the patient made an excellent recovery.

areas of the skin where there is an existing eczema, which may be chronic, or it may appear at sites of dermatitis.

Herpes Zoster

Generally very little thought is given to herpes zoster as a communicable disease. Nevertheless, its relationship to varicella is interesting. If an individual has never had chickenpox or herpes zoster, and is exposed to the latter disease, what appears to be typical chickenpox may develop. Therefore, in an institution for children, there should be strict isolation of anyone who has herpes zoster.

Herpes zoster is almost inevitably a unilateral disease. Exceptions have been reported very rarely. It would seem that a correct visual diagnosis in almost every instance could be made at a glance. But many times this disease is confused with erysipelas, and it occasionally has been confused with cavernous sinus thrombosis. Because of pain, which is often severe, the presence of some other pathologic condition has been suspected depending on the location of the lesions. A heart attack and stone in the ureter are among the causes that have been considered responsible for the pain which was due to herpes zoster.

Herpes zoster may occur at almost any age. Figure 1 is a striking illustration of the unilateral distribution of lesions. For a time it was feared that serious injury to the eye might occur. However, the girl made an excellent recovery at Cook County Contagious Disease Hospital.

Measles

It would seem that measles need scarcely be mentioned here because, as is often said, "anybody can make a diagnosis of measles." Nevertheless, those who have had considerable experience in a contagious disease hospital will admit that such is not the case. But, of course, if Koplik's spots are detected, the diagnosis of measles is simple.

Rubella

One of the most serious decisions that a physician may be called on to make is to decide whether a woman who is pregnant, especially during the first trimester, has measles or rubella. Sometimes this is a very difficult problem to solve solely on a visual basis, because the rash of rubella displays considerable variation. When typical, it is lighter in color than a measles eruption, the lesions are smaller, and they are more diffuse. Usually, the conjunctivae do not have the deep cherry-red color which is almost characteristic of measles. The enlarged postauricular and suboccipital lymph nodes which can often be observed as well as palpated are the outstanding accompaniment of rubella.

Scarlet fever, smallpox in its early prodromal stage, meningococcic or staphylococcic septicemia, urticaria and various drug eruptions have been mistaken for measles or rubella. In addition, the rash which sometimes accompanies mononucleosis and the eruption of secondary syphilis may be mistaken for rubella or measles.

Mumps

Mumps cannot always be diagnosed visually for a number of reasons. Swelling of the pa-

rotid glands can be caused by certain metals, e.g., mercury, lead and the iodides. Moreover, enlargement of these glands is a very common complication of acute systemic infection although it is not necessarily a part of the disease. Mumps usually involves both of the parotid glands; therefore, if only one of the glands is swollen, some thought should be given to the possibility of blockage of Stensen's duct. It rarely will be found that an abscess in or near the gland or perhaps a tumor is responsible for the enlargement of the gland. Palpation should be helpful in clarifying the diagnosis. If palpation discloses fluctuation, it will rule out the presence of mumps, which is a nonpurulent disease.

In some cases of mumps, the involvement is limited to the submaxillary or sublingual glands. In rare cases, the thyroid gland is involved and swelling may occur in the suprasternal area. Mononucleosis and cervical adenitis may produce a clinical picture suggestive of mumps, but the differential diagnosis usually can be made by palpation. In cervical adenitis and mononucleosis, tissues feel indurated; in mumps, they are pliable.

It is generally recognized that there is some relationship between the parotid glands and the sexual organs. Furthermore, swelling of the parotid glands occurs occasionally following a surgical procedure in the perineal region and produces a characteristic clinical picture of mumps. However, gentle massage of the parotid glands may cause pus to extrude from Stensen's ducts.

There is still another condition which is particularly deceptive, and it is one with which all physicians do not seem to be familiar. This is recurrent parotitis. This is a condition in which there is periodic swelling of the parotid glands. Episodes of this kind may occur two to three times a year or more often. There is no redness of the skin, yet the enlargement of the glands has been attributed to such organisms as streptococci and staphylococci. Recurrent parotitis undoubtedly accounts for the fact that some patients say that they have had mumps once or twice before.

From the foregoing discussion one should conclude that a diagnosis of mumps, like the diagnosis of measles, is not always a simple matter.

Scarlet Fever

Scarlet fever is one of the bacterial diseases in which clinical observation may be very helpful in establishing a diagnosis. A prompt decision is also extremely important in order to prevent the transmission of a communicable disease to susceptible persons who have been in contact with the patient.

This formerly was a very serious disease because complications were frequent and caused death or often produced some permanent disability. At present, the disease is mild in this country, and it rarely causes death or serious complications. Those who seem to be most intently concerned about this disease are physicians who have devoted a great deal of attention to rheumatic fever. It is known, however, that rheumatic fever does not develop in every case of scarlet fever, and that a history of scarlet fever is not obtained in every case of rheumatic fever.

At present the diagnosis of scarlet fever is not likely to be made as readily as it has been in the past. Most patients do not appear to be very ill, the eruption is seldom pronounced, and, as a consequence, desquamation may not be observed. In the classic form of the disease, the circumoral pallor is, of course, characteristic, and the eruption which is most pronounced on the trunk fades on pressure. However, there is at least one valuable sign which can usually be detected even in mild forms of the disease. This statement refers to the tongue.

On the first day of a scarlet fever eruption, the tongue is coated and the enlarged papillae protrude and produce the strawberry tongue. On the second day (48 hours from the onset), it will usually be noted that the coating is clearing from the tip and sides of the tongue, and, by the end of three full days, the tongue is generally clean. It is red, and the enlarged papillae are clearly evident, especially if viewed laterally, rather than by looking straight down on the tongue. This is the so-called raspberry tongue which is not observed before at least three days have elapsed since the onset of the eruption on the skin.

The appearance of the tongue in cases of scarlet fever is often a valuable aid in detecting persons who have been exposed to the disease. If the mother states that the child "just broke out today," and yet the patient has a raspberry tongue, the mother is mistaken. The disclosure of her error may mean that a number of individuals to whom the mother has given no thought have been exposed to this infection.

Infrequently, scarlet fever and measles eruptions must be differentiated, and the tongue in cases of the latter disease may closely resemble the raspberry tongue of scarlet fever. However, the measles rash predominates on the face, whereas in cases of scarlet fever the face is flushed, but a finely pinpoint papular rash and the customary subcuticular flush are scarcely ever present in that locality.

Various allergic reactions have been mistaken for scarlet fever. Arsenic intoxication can produce a skin eruption which closely simulates that of scarlet fever, and the prodromal eruption of smallpox, which is not common, may resemble that of scarlet fever, although it is more likely to suggest measles.

Diphtheria

If diphtheria always were diagnosed promptly, and if antitoxin could be given on the first day of the illness, there would seldom be any fatalities. But the onset is insidious. A sore throat is not a prominent symptom as it is in cases of acute tonsillitis. Moreover, the temperature is generally lower than it is in most cases of acute infection. Backache is a fairly common complaint of adults. If the patient happens to be a woman, a careful examination of the abdomen may be made, but perhaps no inspection of the throat. In every case of illness, the oral cavity including the throat should be examined.

If there is a heavy membranous material on the tonsils which stops short of the tonsillar pillars, it is almost certain that the condition is not due to diphtheria. Sometimes the throat of a patient with mononucleosis looks very much like the throat of a patient with diphtheria. Also, the lymph nodes of the neck are likely to be greatly enlarged, and a clinical diagnosis of so-called bull-neck diphtheria may be made erroneously. The presence of this disease can easily be ruled out even before inspection of the throat. On palpation of the neck in cases of mononucleosis, the lymph nodes are indurated and hard; in cases of bull-neck diphtheria, the tissues of the neck are comparatively soft and pliable. Furthermore, a patient with bull-neck diphtheria is almost certain to have a nasopharyngeal involvement and a serous discharge from the nostrils. The nasal discharge has in the past frequently explained the tardiness in diagnosis. The mother often has thought that the child simply had a cold, and, therefore, failed to call a physician promptly. In cases of bull-neck diphtheria, the breath often has a fetid odor, which has seemed to be diagnostic of this type of the disease. The odor can be detected at some distance from the patient. In the early stages of this type of diphtheria, the disease occasionally has been mistaken for mumps, and the outcome has been disastrous owing to the delay in instituting treatment.

Meningitis

This is another disease in which there may be valuable signs that will cast light on the etiologic factor. If petechiae are present in the skin, it is almost certain that the *Meningococcus* is the etiologic organism. Petechiae seldom occur in any other type of meningitis. If petechiae are not present but chronic otitis media is detected, the presence of a pneumococcic infection should be suspected. The same holds true if there is evidence of an old skull fracture or some other head injury. Age may also deserve some consideration. If the patient is an infant or a young child and if there are no petechiae, one first should consider the possible presence of a *Hemophilus influenzae* infection. In about 90 per cent of all cases of influenzal meningitis, the patients are less than five years of age. This type of meningitis is observed with extreme rarity in adults.

Usually, an examination of the eyes is not helpful in the diagnosis of meningitis. Nevertheless, in cases of tuberculous meningitis, it is not uncommon to find an inequality of pupils, especially in children. This disclosure is

one that is hardly ever made in other types of meningitis. Of course, an abscess or a tumor may account for this finding when meningitis is not present.

Erysipelas

As in the case of scarlet fever, the decline in the incidence of this streptococcic infection has been remarkable. And there is no reliable method for immunization against erysipelas. Furthermore, one attack seems to predispose another. The sharp line of demarcation observed as the inflammatory area of the skin spreads is regarded as characteristic. If the ears are involved, they are not merely red, but swollen and misshapen, as they sometimes are in a professional wrestler or a leper. In the last case of leprosy seen in Cook County Contagious Disease Hospital the patient was a woman who was sent there as an erysipelas patient. The leprosy was found to be in a far-advanced stage.

Whooping Cough

Little mention need be made of pertussis unless one is to question the possibility of parapertussis. But a diagnosis of the latter disease is not made very often. In other words, parapertussis is uncommon. Therefore, the characteristic cough is generally sufficiently convincing as evidence of whooping cough.

Poliomyelitis

A great many errors are made in the diagnosis of this disease. But, of course, some are pardonable when the diagnosis is made in the home without the aid of hospital facilities. Nevertheless, for many years, I have believed that there are two signs which are of the utmost value. Moreover, no complicated technic is required for their elicitation. First, there is the head drop. With the patient lying supine, the examiner places his hands behind the patient's shoulders and slowly raises his body. Then, as the body is elevated, the patient's head either drags on the bed or he raises it with difficulty, but cannot long support it in the plane of the body if he has poliomyelitis—and the head falls back. The other sign is simply stiffness of the neck which is easily detected by flexing the patient's head toward the chest.

The two signs are nearly always present during the first two or three days of the illness and may persist for a week or 10 days, or even longer. Occasionally, if head drop is present, the neck sign is absent, but stiffness of the back serves as a good substitute. These signs are present in nearly every case of poliomyelitis regardless of whether the disease is paralytic or nonparalytic. Consequently, if they are absent, there is small chance that the patient has poliomyelitis.

Comment

Careful observation is important in the clinical diagnosis of many infectious diseases. If possible, however, the diagnosis always should be based on the result of laboratory tests. A history also may be of great value if it is reliable, but no one can be deprived of knowledge acquired by vision.

Obesity in Children and Adolescents

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OBESITY in a child represents many baffling problems. Even though there are not many physical complaints that can be directly related to the burden of weight, there are few conditions that cause as much misery and unhappiness. Fat children are likely to become the object of ridicule, and they feel socially isolated and excluded from the games and activities of their age group. Matters become worse during adolescence when social activities and the relation to the opposite sex gain in importance. One should expect that the victims of this condition would make every effort to follow instructions designed to make them lose the excess weight. Yet "failure to cooperate" overshadows the whole course of events. If parents try to enforce the prescribed diet, fat children and adolescents are likely to turn in defiance against them, will eat even more, and thus grow progressively fatter.

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This skeptical approach to the treatment of obese children and adolescents runs in many ways contrary to the prevailing medical concepts that obesity is simply the result of a positive energy balance and could and should be treated by establishing new and better eating habits. Theoretically, this is correct, but in practice there are endless difficulties against the effective use of our reasonable and adequate nutritional knowledge. The many problems involved in a realistic and constructive approach to obesity have been developed in detail in a recent book elaborating on the importance of overweight.[1]

I should like to illustrate through the following case history the extent to which the inability to follow a diet is an expression of the interaction of many emotional problems and difficulties within a family.

Shirley, 11 years old, was an only child who lived with her parents and grandmother in a

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modern home in an upper middle-class suburb. The grandfather had also been part of the household until his death a few years ago. The child was seen in psychiatric consultation in 1950. She had been fat, or at least chubby, as far back as anybody could remember, in spite of continuous efforts to make her reduce. Her highest weight had been 140 lb.; at the time of the consultation, it was only 125 lb. The parents had been married for 15 years, and the mother had continued to work as a social worker. She had taken maternity leave and had returned to work when the child was a year and a half old, and the grandmother had taken care of the girl. The additional income was needed to pay for the beautiful home. When Shirley was five years old, her grandfather had a heart attack and needed the constant attention of his wife. The mother took a year's leave and went to Florida with the daughter who then became really fat. The mother was advised not to give her ice cream and sweets, but she did not have the heart to "deprive her."

In spite of the obvious reason for the rapid increase in weight, one physician attributed it to a "glandular condition" and treated her with injections and other medications. The parents became convinced that the fatness and the child's behavior difficulties were due to the "sluggishness of her glands." They returned to New York, and she was taken to another endocrinologist. The weight continued to increase rapidly in spite of the prescription of diets and continuous glandular injections.

Meanwhile, other difficulties developed, such as extreme defiance and stealing. Psychiatric help was recommended by the school when Shirley was seven years old. Resenting this, the mother chose not to follow the advice. Instead, she took the child to another endocrinologist who also gave injections. It is puzzling how intelligent parents would continue this regimen even though the child became visibly fatter. Her weight was 100 lb. when she was eight years old.

The complaints from the school continued and became more urgent. The girl would steal and lie, was excitable, would scream and wanted her own way at all times, and did not get along with other children. There were also many difficulties in camp. Shirley had attended the same camp for several summers, although the mother complained each year about the lack of understanding on the part of the counselors. Since the weight continued to increase, the parents consulted another physician who, however, did not give injections but insisted on psychiatric treatment. It took the parents a whole year before they came for a consultation.

This was obviously a situation in which nothing could be accomplished unless the parents gained some understanding of their role in the girl's difficulties. The father was exceedingly reluctant to assume any responsibility. He took the attitude that everything was to be blamed on the grandmother's presence in the home, and that nothing could be done as long as the old woman ran their lives. She had done so since his marriage. The mother was now extremely eager for help and wanted it immediately. She had applied to a child guidance agency and was indignant that there was a waiting list.

The mother had gone out of her way to appease the school and the camp, in spite of her making special demands of them. Part of this mother's confusion was related to her being perplexed about her role as a mother while she still submitted to her own mother and in relation to whom she played a child's role. The grandmother was fond of Shirley in her own way, which expressed itself in being very ambitious for the child. The grandmother stressed excellent manners, neatness and good clothes, etc., so that the child would be an outstanding child in her well-to-do community. Thus a great deal was expected of the child, but she never received any consistent discipline nor did she have to face the consequences of her misbehavior. There had been no need for the child to develop controls from within or even a concept of self-restraint. Her inability to follow dietary restrictions was just one aspect of this severe maldevelopment.

The child felt that there was nothing wrong with her life. Thus far she had been able to get her way, and whenever she felt frustrated she would shout and cry, and make a scene.

She was a very fat, sulky girl, who was tall for her age and condescending in her total attitude. She definitely was not interested in what psychiatry might have to offer. She felt that her teacher's poor opinion of her did not count and that the camp director's complaints were due to the unjust reports given by the counselors. She appeared to be quite satisfied with the role she played in her home where she was the dominant and most powerful figure. She had an overinflated feeling of her own importance, and there was little or no intent of changing anything about the present situation.

A Rorschach test confirmed the clinical impression, namely, that of severe emotional immaturity with a type of self-centeredness and impulsiveness usually observed only in much younger children. There were signs of aggressive and destructive impulses, but also on a very immature level. Emotionally, she was isolated and showed no ability to establish human relationships, except through defiance and aggression. It was discussed with the parents that in view of the serious disturbance there was need for a re-evaluation and improvement of the attitudes of the whole family group. The mother objected immediately that she could not see why so much treatment was needed which might take a long time. Even though the mother had been impatient to get help, contact was broken after a few visits; she wanted a child who would become slim, but she shrank from a decisive change in her or anybody else's attitude.

The parents came for another consultation six years later, in 1956, when their daughter was 17 years old and in her senior year in high school. They had made many more efforts at finding help. They usually had taken their daughter to endocrinologists or "reducing doctors"; twice more they had tried psychiatric help, but had discontinued it after a few visits. Now they were panicky because they feared that the girl was on the verge of a nervous breakdown. She had continued to be exceedingly negativistic, would never accept anybody's advice or suggestions, and refused to take on any responsibilities for ordinary chores. The grandmother had died a year ago, following which the girl's behavior had changed. She developed certain perfectionistic traits. She would spend as much as three or four hours in getting ready for a date, and she was not satisfied with her school work unless she got an A in every subject. However, when she stayed at home, she would not dress at all, and her room was always dirty and untidy. She refused to go to school when she felt upset, and she would also stay away when there were tests.

The girl's attitude toward her obesity and her eating pattern had also undergone a change. She was now concerned about being too fat, and gave her ugly appearance as a reason for keeping so much to herself. She complained that her obesity kept her from having as many dates as she wanted. She was not popular in her class, but a few young men whom she had met outside the school would take her out.

On coming home from a date she would be excited, feel unable to sleep, and begin eating enormous amounts. Sometimes she would not go to bed until the early morning hours, and would sleep all day on Sunday and would get up only to gorge herself with more food. She often spent Monday in the same way, eating and sleeping. During the past few months a definite cycle of "feast or famine" had been established. In order to lose weight, she had gone to a physician who gave her "reducing pills" (amphetamine) and advised her about a diet to which she did not adhere. She would spend the first three or four days of the week sleeping and eating without any control, consuming whatever was available (a quart of ice cream or a whole loaf of bread, even dry bread, in one sitting). She would be more spiteful toward her parents than usual, would not dress or comb her hair, would be exceedingly preoccupied and often would not respond at all. She would gain as much as 10 or 15 lb. during such an eating spree, and then become disgusted with her bloated appearance and stop eating altogether.

She would take five or six of the reducing pills, constantly increasing the doses until she was so excited that she could not sleep. She would not eat, and thus would lose most of

the weight accumulated during the early part of the week. The parents were indignant, and it seems with justification, about the physician who continued to supply her with amphetamine tablets even though they had informed him of the unhealthy use she made of them. Her weight increased continuously and fluctuated between 180 and 200 lb. She had grown very little in the past six years, and she was a short and extremely obese girl. Menarche had occurred at age 12 years.

The total picture had deteriorated to such an extent that it seemed unlikely that she could be treated and that the addictionlike habituation to the amphetamines could be interrupted while she remained in the home environment with all the pressures and tensions of mutual hostile distrust and the increasing sense of futility.

This story of therapeutic failure over many years is unfortunately not unique in cases of childhood obesity. In this case, it would be tempting to blame the parents' attitude for the disastrous course of events. This certainly played a role, but it represents only one side of the problem. Their inconsistent behavior was aided and abetted by conflicting medical advice. Whenever one physician outlined a treatment program to correct the severe emotional involvement of the whole family, there was always another ready to promise a "get-thin-quickly" cure through glandular injections, diets and reducing pills. This confusion in the medical approach adds to the perplexities of a family faced with the problem of obesity in a child. The prevailing medical approaches do not take sufficient notice of the extraordinary close interaction between physiologic and psychologic factors in the development and treatment of obesity.

It is easy enough to produce remarkable loss of weight through dieting and increased physical activities, even though there are many cases in which even this cannot be accomplished. It requires psychologic awareness, skill and patience to help a child accept the necessity for changes in his eating habits—and even then results are often short-lived. It seems to be well-nigh impossible for a child or adolescent to maintain a lower weight *unless there is a true change in his psychologic adjustment*. This statement is based on observations made on a large group of obese children whose development has been followed over nearly 20 years. These children were first observed between 1937 and 1940 at the Babies Hospital in New York. In all of them obesity, usually of severe degree, had developed before the onset of puberty. The physiologic and psychologic aspects of the development of these children have been described in great detail.[2-6] When this study was undertaken, it was commonly believed that obesity in a child was caused by hypofunction of the thyroid or pituitary gland or both. It could be demonstrated in this group that this whole approach to the obesity problem was wrong.

Obese children are not delayed in physical growth and maturation, as they would be if they were suffering from hypothyroidism or hypopituitarism; on the contrary, they tend to be taller and broader than their age peers. Skeletal maturation as determined by roentgenograms is also advanced, and stands in good agreement with the accelerated statural growth. Of greatest practical importance is the fact that puberty occurs at a normal, or often early, age in both obese boys and girls. The diagnosis of hypogenitalism often is made erroneously when fat pads in the pubic region mask the true size of the genitalia. Cryptorchism is as rare in obese as in nonobese boys, and adequate genital growth during puberty will occur spontaneously. In spite of this evidence, which has been confirmed by many other observers, there are physicians who continue to make the diagnosis of an endocrine disorder on the basis of exceedingly vague symptoms and who give glandular injections to the detriment of the child and the exclusion of a more constructive treatment approach.

Recent investigations suggest the possibility of an endocrine involvement, but of an entirely different order. The growth factor (somatropin) and the diabetogenic factor of the pituitary body have been recognized as identical. Excessive supply produces accelerated growth in the immature organism, and diabetes in the adult. The frequent combination of diabetes and obesity in the middle-aged,

and of advanced growth and early maturation with obesity during childhood, may thus be related to some common factor which would indicate hyperactivity of the pituitary body, and not hypofunction, as has been postulated in the past.

At present, the predominant clinical approach conceives of obesity as resulting from a positive energy balance; which means children (and adults, too) grow fat when their food intake exceeds the energy expenditure for the life processes and physical activity. Exercise and reducing diets are considered adequate treatment for the condition. This they are—at least on paper. This approach to the obesity problem deals only with the obvious; it does not include the fact that obesity is a far from simple and uniform condition.

Overweight and obesity do not represent a disease entity, but they are symptomatic expressions of a variety of underlying disturbances in the weight-regulatory mechanism. This is a complex function, even in the normal child, and it can be interfered with in many ways. This has been extensively demonstrated in animals, and a variety of metabolic disturbances have been described for the different types of animal obesity.[7] No such clear-cut differentiation is possible, at this time, for human obesity. But clinical evidence suggests that there are distinct differences in the weight development and eating patterns of patients with different forms of obesity.

In the follow-up study at Babies Hospital, at least four different patterns of development could be recognized. In many children, remarkable losses of weight had been achieved, and it had been expected that they would stay slim and have a normal development. This hope was not fulfilled. By following these children into adulthood (their age range now is from 18 to 30 years), it was found that the early efforts of reducing had had little or no influence on the development. Externally enforced reducing may interrupt but does not alter the basic pattern of an individual's weight curve. In many cases, preoccupation with weight and dieting had become the focal point of serious emotional conflict.

Quite early in the study, the extraordinary emotional involvement of the parents, usually the mother, was recognized.[8] This was expressed in exaggerated concern with the physical well-being of the child, the most conspicuous manifestation of which was overstuffing him with food and shielding him from all physical dangers, which resulted in enforced inactivity for the child. There was marked resistance against following the seemingly rational advice of "eat less and exercise more." The children as well as the parents reacted as though they felt threatened. Even though being fat represented a serious emotional and social handicap, it became apparent also that it played a definite positive role in maintaining a precarious adjustment to life.

The extent of this protective function was fully appreciated only by observing the development over many years. The findings were analyzed according to persistence or absence of overweight, and according to the over-all psychologic adjustment. Four possibilities exist for their combination: (1) slenderness with good adjustment; (2) slenderness with poor emotional adjustment; (3) continued obesity with good adjustment; and (4) continued obesity with maladjustment. All combinations were observed.

It is of practical importance that it is possible to predict the long-range development with a fair degree of accuracy through a comprehensive evaluation during childhood. This should include an assessment of the emotional problems of the obese child and his interaction with his family, and the evaluation of his weight curve and its stability or fluctuations. The amount of overweight is less important, even though severe degrees of obesity usually indicate serious maladjustment. In no case was there a favorable outcome when emotional disturbances had been recognized but adequate psychiatric treatment had not been carried out. The case presented at the beginning of this paper was intended as an example of this resistance against psychiatric help.

An embarrassing contrast between the amount of medical treatment and the later development became apparent. A favorable outcome, that of slenderness or moderate obesity with good social adjustment, was achieved

only by those who had had the least amount of medical attention, no endocrine injections, and no enforcement of dietary restrictions. These patients had established control over their weight during adolescence, or in early adult life, on their own initiative, not under outside compulsion. In the other groups, efforts at dieting had increased the constant fighting in an already overstrained family situation or the strain of dieting, even though self-imposed, had reinforced existing psychologic problems. The result was unfavorable total development, despite temporary weight loss.

Even poorer was the effect of continued endocrine treatment. The patients who had received the largest amount of endocrine products were suffering from the more severe forms of mental disturbance, such as frank psychosis. This, of course, was not produced by the endocrine injections themselves. Parents who are dissatisfied with or anxious about a child's atypical development will continuously search for the kind of treatment that promises to alter and transform the child, and they are likely to resist an approach directed at their own disturbed involvement. Such continued pressure and discontent may become manifest in a child as severe mental illness, even psychosis.

In stressing the poor results of the conventional treatment approach to obesity, I do not wish to imply that obese children cannot or should not be treated. Progressive obesity in a child or adolescent is always a serious disorder, and successful treatment is not possible unless the underlying difficulties are correctly diagnosed and adequately treated. The fact that this is not a simple task is no justification for the seeming short cut of attacking the weight directly. Even a fairly well-adjusted person will find it difficult to carry through a reducing regimen and can do so only with proper support and instruction. In the presence of emotional problems, there is danger of precipitating more serious disturbances.

Fat children and adolescents often expect that all their problems and unhappiness will be solved once they lose weight. Many adults, including physicians, share this false optimism. Reducing undertaken in the hope of transforming the whole of life into a glamorous existence is bound to meet with failure. The problems may be so serious that the help of a psychiatrist will be needed. It is necessary to inform the child and his parents that psychiatric treatment has as its goal the resolution of emotional conflicts and interpersonal difficulties; it is not a special trick to persuade a reluctant fat patient to stop eating. However, it can help a fat child to be successful in his struggle to dissolve the overintense ties to his parents, to achieve true independence and a sense of identity, and thus become able to control his weight.

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Hermaphrodism and Pseudohermaphrodism in Children

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WHEN an infant is born with an evident abnormality of the external genitalia, the disturbed parents turn to the general practitioner, pediatrician, or surgeon, rather than to the endocrinologist, for advice and guidance. They feel responsible for what has happened and may suspect a hidden sexual abnormality in themselves. They may believe that the child will become a sexual pervert in later life. They often fear the social consequences of this birth. Unfortunately, the physician whom they first consult is also frequently in doubt about the problem with which he is presented and how to deal with it. What he may say or do before asking for an expert opinion may have far-reaching consequences. If he frankly conveys his uncertainty to the parents, or if he waits "to see what will happen," he may make the already difficult situation worse by amplifying the parents' inner doubts. If, instead, he ignores the problem and arbitrarily decides on the basis of a superficial examination that the infant is in fact a male (or female) and should so be reared, he may consign the individual to an unsuitable gender role.

Neither the definition of nor the solution to this problem is simple. There are several reasons why this is so. First, direct inspection of the external genitalia cannot establish with certainty the true sex of these individuals, the nature of genital malformation, or its cause. Second, even inspection of the internal genitalia at laparotomy without biopsy of both gonads may lead to gross errors in diagnosis. Third, the histologic appearance of the gonad may not necessarily conform to the type of

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hormone which the gonad produced in utero or will subsequently secrete when adolescence is reached. Finally, the psychologic orientation of the individual as male or female is frequently at variance with the structure or hormonal function of the gonads, and is, instead, primarily directed by environmental attitudes during the first two or three years of life.[1]

Out of this confusion of complicated terminology, nondiagnostic physical findings and psychologic disturbances, a measure of order can be created. This requires a brief review of embryology, the establishment of a working classification of the common genital malformations met with in practice, an outline of the diagnostic tests available, and a discussion of the management of patients both before and after the diagnosis has been established.

Embryologic Background

The differentiation of the human gonad and the development of the internal and external genitalia begin during the second fetal month, and are largely complete by the end of the third. Until this time, the two sexes cannot be differentiated: In both there are histologically indifferent gonads and paired accessory ducts, the mesonephric-wolffian (male) and muellerian (female) systems. The direction which development will normally take depends on the genetic make-up of the individual. Inheritance of a Y-chromosome from the father and an X-chromosome from the mother produces a genetic male whose gonad will become a testis and whose genitalia will develop in the masculine direction; inheritance of an X-chromosome from both parents creates a female. The gonad which is to become a testis differentiates first, in the eighth week of fetal life. Some secretion of the fetal testis apparently organizes development of the accessory ducts in the masculine direction. The muellerian system degenerates, and the wolffian system grows to become the epididymis and seminal vesicles. After testicular function begins, the phallus also starts to develop, and the urogenital sinus is incorporated into the phallus, producing a penile urethra. Under the influence of a testicular secretion, the scrotum forms, but not until the end of fetal life do the testes descend into it. Following birth, the testes remain inactive until adolescence.

In the female, gonadal differentiation begins one or two weeks later in embryonic life. It is probable that the fetal ovary does not secrete an organizing hormone itself, but that maternal estrogens are responsible for normal feminine development of the internal genitalia. Removal of the ovarian anlage does not interfere with this course of events. The opposite is true in the case of the testis: Damage to or removal of the testis during the critical developmental period invariably leads to feminization of the genital tract. Accordingly, the muellerian ducts develop to form a uterus and tubes in either the genetic female or the genetic male unless the effect of maternal estrogens is opposed by a male-type hormone produced by the fetal gonad (testis). Without androgen stimulation the wolffian ducts degenerate. This lack of gonadal androgen secretion in the normal female fetus would seem to explain the lag in the development of the phallus, which remains small, the failure in the female of the urogenital folds to form a urethra inside the phallus, the failure of the genital swellings to fuse in the mid-line to form a scrotum—instead they remain open, as the labia majora—and perhaps even the failure of the ovary to descend into the labia.

It is not surprising that such a complicated sequence of developmental events can be interrupted or disturbed to produce a large variety of genital abnormalities. The factors involved are only partly understood. If the testis is unable for some reason, such as a genetic defect, to produce the male-type hormone in utero, the wolffian system will degenerate and the muellerian survive, producing a femalelike genital tract in a genetic male. In contrast, some other source of androgen may disturb the genital development of the female. Androgens produced by an arrhenoblastoma of the maternal ovary (rare) may counteract the effect of maternal estrogens and produce masculinization of the internal and external genitalia. Much more commonly, in congenital adrenal hyperplasia, androgens produced in the fetal adrenal cortex bring about such changes.

TABLE 1

CLASSIFICATION OF HETEROSEXUAL DEVELOPMENT

CLASSIFICATION	OTHER COMMON NAMES	FREQUENCY	ETIOLOGY	EXTERNAL GENITALIA	OTHER PHYSICAL FINDINGS
. Congenital					
A. Female pseudohermaphrodism					
1. Adrenal ("sex reversal")	Adrenogenital syndrome; congenital adrenal hyperplasia	Common	Adrenal hyperplasia due to enzymatic defect	Usually, urogenital sinus; hypertrophied clitoris	Somatic overgrowth; advanced bone age; precocity
2. Nonadrenal ("intersex")		Very rare	1. Genetic (?) 2. Maternal arrhenoblastoma	Same as in adrenal type, or penile urethra	Normal growth
B. Male pseudohermaphrodism ("intersex")					
1. Gonadal dysgenesis	Ovarian agenesis; Turner's syndrome	Common	Gonadal dysgenesis of unknown cause	Normal female	In child or adult, short stature, web neck, coarctation, etc.; in infants, Bonnevie-Ullrich syndrome (edema)
2. Gonadal dysfunction	Feminizing testis syndrome	Common	Genetic (?)	Normal female or hypospadias and cryptorchidism, or urogenital sinus	Abdominal or inguinal testes (hernia); normal growth
C. True hermaphrodism ("intersex")		Relatively rare	Genetic	Any variant of above	Normal growth
:. Acquired ("sex reversal")					
A. In female	Adrenogenital syndrome; virilized female	Rare in childhood	Adrenal tumor or hyperplasia	Hypertrophied clitoris but *no* urogenital sinus	Somatic overgrowth; advanced bone age; precocity
B. In male	Feminized male	Very rare in childhood	Adrenal tumor; chorioepithelioma	Normal, or testicular tumor	Gynecomastia; advanced bone age

Classification and Diagnosis of Common Genital Malformations

Table 1 offers a working classification of the common types of ambiguous development of the urogenital tract seen in clinical practice. For the sake of completeness, it includes abnormalities acquired after birth as well as malformations which are evident at the time of delivery, and those not evident by inspection, hence usually undiagnosed in infancy, but which properly belong in the category of congenital disease. The table indicates the two widely used classification systems. The first divides all types into true hermaphrodism and pseudohermaphrodism. A true hermaphrodite

TABLE 1 *(continued)*

CLASSIFICATION OF HETEROSEXUAL DEVELOPMENT

ROENTGENOLOGIC FINDINGS	CHROMOSOMAL "SEX"	URINARY EXCRETION OF STEROIDS		GONADAL BIOPSY	SECONDARY SEXUAL DEVELOPMENT	REMARKS
		17-Ketosteroids	*Pregnanetriol*			
Urogenital sinus, vagina, cervix	Female	High	High	Ovary normal	Masculine if untreated	Inherited defect of hydrocortisone synthesis effectively controlled by cortisone. Patients may have salt-losing tendency
Same as in adrenal type	Female	Normal	Normal	Ovary normal	Normal female	Diagnosis may be cryptorchid male with hypospadias
Normal female	Male	Normal	Normal	Rudimentary testes previously thought to be ovaries	Imperfectly feminine; scanty pubic hair; poor breast development; amenorrhea	Incorrectly called ovarian agenesis in past. High FSH titer after 10 to 12 years. Dysgenesis of fetal ovary produces same picture
Blind vaginal pouch or normal female	Male	Normal	Normal	Immature testes	Imperfectly feminine; amenorrhea	Frequently familial; testes often secrete estrogens; FSH normal
Any variant of above	Male or female	Normal	Normal	Rarely testes and ovary; usually ovotestes	Unpredictable; either masculine or feminine	Diagnosis established only by gonadal biopsy
	Female	Usually very high; excretion of dehydroepiandrosterone often high with tumor	Usually normal with tumor; high with hyperplasia		Progressive virilization	Acquired hyperplasia very rare in childhood (suspect tumor); hirsutism alone rarely signifies virilization or adrenal disease
	Male	Normal or high			Progressive gynecomastia	May be confused with adolescent gynecomastia or Klinefelter's syndrome in older children

is an individual with both male and female type gonads, variously malformed but most commonly consisting of ovotestes, and ambiguous external genitalia. The male pseudohermaphrodite is a genetic male with testes, often malformed, and ambiguous or frankly feminine-appearing external and internal genitalia. The female pseudohermaphrodite usually has normal ovaries but external genitalia resembling those of a male.* This group of diseases can also be divided into sex reversals and intersexes.[2] The former are due to dysfunction of an endocrine gland before or after birth;

*Some examples of Klinefelter's syndrome are female pseudohermaphrodites, according to recent studies.[3] This condition is not discussed here.

FIGURE 1. Typical appearance of external genitalia in case of female pseudohermaphrodism due to congenital adrenal hyperplasia. Hypertrophied clitoris, scrotal-appearing labia majora, and urogenital sinus may be noted. This illustration should be compared with figure 2.

FIGURE 2. Close-up view of external genitalia of a male pseudohermaphrodite. Appearance of the phallus and urogenital sinus is indistinguishable from that in figure 1.

in the latter, no endocrine dysfunction is demonstrable. The most common example of a sex reversal is female pseudohermaphrodism due to congenital adrenal hyperplasia, which begins in intra-uterine life and continues after birth. There is one other much rarer, self-limited congenital form, namely, virilization produced by a maternal arrhenoblastoma. Acquired forms of sex reversal may be due to disease of the ovary, adrenal glands, or testes, and will not be discussed at length.

In attempting to diagnose the type and cause of ambiguous sexual development seen in the infant, the endocrinologist properly begins with a detailed history. It is important to learn whether there have been genital malformations such as this or of other types in members of the family. If one obtains the history of a sibling with a genital abnormality, particularly if that infant died shortly after birth, one should suspect the presence of congenital adrenal hyperplasia in the patient. However, if one obtains a history of genital abnormalities in previous generations or in collaterals, this is not suggestive of congenital adrenal hyperplasia, but rather of male pseudohermaphrodism or true hermaphrodism. One wishes to find out whether the pregnancy was entirely normal. Several examples of maternal arrhenoblastoma have been retrospectively diagnosed after the birth of a virilized female infant. Profound nutritional disturbances in pregnant animals may produce genital abnormalities in the offspring, but this occurrence has not been reported in man. If one is dealing with an older child, one should ask about the appearance of the genitalia at birth and, subsequently, the rate of body growth, and the age of the appearance of secondary sex characteristics. A history of progressive heterosexual development signifies a form of sex reversal.

After the history has been obtained, a careful physical examination is performed. Dehydration in an infant with a genital abnormality may be due to the salt-losing form of congenital adrenal hyperplasia. In an older child, the triad of genital abnormality, premature appearance of pubic hair, and somatic overgrowth should also lead the examiner to suspect the presence of adrenal disease. Careful examination of the external genitalia is, of course, essential. The phallus is examined first.

It may represent a maldeveloped penis or a hypertrophied clitoris. The presence of a penile urethra does not rule out female pseudohermaphrodism, but does suggest male pseudohermaphrodism. Most commonly found is a single perineal orifice at the base of the phallus from which the child or infant micturates. The opening may represent the urethral orifice in a hypospadiac but otherwise normal male (a diagnosis which needs to be proved if the gonads are not palpable) or a urogenital sinus. The presence of a urogenital sinus means only that the genital disturbance began in fetal life; it does not establish the diagnosis. Figure 1 illustrates the typical appearance of the hypertrophied phallus and the urogenital sinus in female pseudohermaphrodism due to congenital adrenal hyperplasia. It will be noted in figure 2 that the same abnormality may be seen in male pseudohermaphrodism, as it may also in true hermaphrodism.

The configuration of the labia or scrotum is next inspected. Hypertrophied labia majora usually encircle the phallus superiorly (figure 1), but it may be difficult to distinguish fused labia majora from a scrotum. The scrotum may appear bifid in a normal male infant, which abnormality by itself does not imply a form of hermaphrodism. The examiner then proceeds to palpate for gonads in the genital folds and in the inguinal canals. A gonad which is palpable is usually a testis, and such a finding is strong evidence against the diagnosis of female pseudohermaphrodism. The gonad however may be an ovotestis in a true hermaphrodite. The absence of testes may simply signify cryptorchidism in the male if there is no other abnormality of the external genitalia. One inspects the perineum for a vaginal orifice and performs a rectal examination (palpable prostate? cervix?).

As noted in table 1, the external genitalia may appear to be those of a perfectly normal female, although the individual is a genetic male in whom a profound disturbance of genital tract development has occurred. Such hidden abnormalities usually are not diagnosed until a later age when a testis presents as an inguinal hernia in a female, an adolescent girl fails to develop pubic hair or to menstruate, or an abdominal operation is performed for some unrelated cause, such as appendicitis.

The physical examination alone is inadequate. At this point the radiologist can offer valuable information by outlining the structure of the internal genitalia, injecting a radiopaque dye such as LIPIODOL® into the perineal orifice. This maneuver has proved superior in our hands to urethroscopy.[4] Figure 3 presents an excellent example of the results of Lipiodol injection. The urogenital sinus is demonstrated (simultaneous filling of vagina and bladder) as well as a uterus and tubes. This picture is that most commonly seen in female pseudohermaphrodism, but this infant proved to be a true hermaphrodite. What, then, one may ask, is the value of radiologic investigation? First, it helps to determine the anatomy of the internal genitalia associated with an external

FIGURE 3. Roentgenogram of internal genitalia made after introduction of Lipiodol through the perineal orifice. Since the Lipiodol outlined the bladder and vagina simultaneously, a urogenital sinus is present. The Lipiodol also outlined the small cavity of the uterus and the dilated fallopian tubes. Finally, Lipiodol was injected through the anus to outline the rectum. The roentgenographic diagnosis was female pseudohermaphrodism; examination of a buccal smear revealed a male chromatin pattern, and gonadal biopsy disclosed ovotestes. The final diagnosis was true hermaphrodism.

malformation. The demonstration of a urogenital sinus proves that one is dealing with a congenital, not an acquired, malformation. The information gained facilitates planning of future plastic surgery.

A second diagnostic procedure is the determination of the chromosomal sex of the individual, most easily done by examination of the buccal smear. The results of testing in the various forms of ambiguous sexual development are listed in table 1. The determination is of limited diagnostic value, for it does not distinguish true hermaphrodism from pseudohermaphrodism. Attention is directed to the potential value of the procedure in the diagnosis of two forms of male pseudohermaphrodism prior to puberty: (1) the syndrome gonadal dysgenesis[5] (formerly called ovarian agenesis) in which the diagnosis is suspected clinically not on the basis of an abnormality of the external genitalia but on such findings as web neck, short stature, coarctation of the aorta, etc., and (2) the familial form of male pseudohermaphrodism, frequently not suspected until puberty.[6,7]

The most important single diagnostic test in the study of this group of malformations is the determination of the excretion of 17-ketosteroids and pregnanetriol in the urine. An elevated excretion is found only in cases of congenital adrenal hyperplasia or acquired adrenal disease. Adrenal tumors do not occur early enough in fetal life to produce such malformations in the newborn as the urogenital sinus. An elevated excretion of pregnanetriol is diagnostic of congenital adrenal hyperplasia and is often a more sensitive index of the degree of adrenal overactivity than the determination of the excretion of 17-ketosteroids.[8] In all the other congenital malformations of the external genitalia, the excretion of these two types of steroids is low, less than 0.5 mg. daily.

In spite of these tests, one is still unable to distinguish true hermaphrodism from nonadrenal female pseudohermaphrodism, which is rare, or from certain forms of male pseudohermaphrodism, which are relatively common. However, one has already accomplished a great deal by ruling in or out the presence of congenital adrenal hyperplasia, for which hydrocortisone treatment is effective in permitting normal growth and development, and even survival.[9,10] If this diagnosis has been eliminated but none other established, one proceeds to the final important diagnostic procedure, exploratory laparotomy and biopsy of the gonads. Specimens of both gonads should be examined. The following case summary illustrates the surgeon's inability to diagnose the true state of affairs by simple inspection of the internal genitalia.

A four day old child was admitted to the hospital because of ambiguous external genitalia. The phallus resembled a hypospadic penis. At the base of the phallus, there was a single orifice from which urine flowed. No diagnostic tests were employed, but a laparotomy was performed. Inspection of the internal genitalia revealed a small uterus, what were thought to be fallopian tubes, and gonads judged to be ovaries because of their appearance and location. Gonadal biopsy was not performed. A diagnosis of female pseudohermaphrodism was made, and the child was reared as a girl. Repeated infection of the urinary tract and hydro-ureters resulted from a stricture of the perineal urethral orifice and necessitated readmission to the hospital when the child was four years old. Examination of the very feminine-appearing "girl" revealed a prominent phallus, a urogenital sinus, and a male chromosomal pattern in the buccal mucosa. The child is accordingly either a male pseudohermaphrodite or a true hermaphrodite, but not a female pseudohermaphrodite. Gonadal biopsy at the time of operation would have established the correct diagnosis.

Treatment of Malformations of the Genital Tract

The diagnostic tests outlined establish in the individual instance whether one is dealing with congenital adrenal hyperplasia. This is extremely important. It is well known that if left untreated all females with pseudohermaphrodism due to congenital adrenal hyperplasia will either die in infancy from a salt-losing tendency, or, not showing such a tendency, will live to become masculinized, stunted,

amenorrheic adults. This unpleasant fate can be averted by early diagnosis and institution of treatment with cortisone. Most commonly the hypertrophied clitoris shrinks in size if treatment is begun early, thus obviating the need for clitoridectomy, and at a later date the urogenital sinus can be corrected surgically. If the diagnosis is made and treatment begun early, the female can be raised as an outwardly perfectly normal girl. If the diagnosis has not been established until a later age and the patient has been raised as a male, it may be inadvisable to start cortisone treatment or otherwise attempt to change the sex.

The treatment of other forms of pseudohermaphrodism and true hermaphrodism is more complicated. It depends first of all on the age at which the child is seen and the diagnosis established. As in the case of congenital adrenal hyperplasia, no attempt should be made to change the gender role to conform to the true sex once the child has passed the age of three or four years. Usually, by this age, the child has a firm concept of being a boy or a girl, a solid emotional foundation which should not be undermined. Accordingly, treatment at this age should merely consist of plastic procedures necessary to permit the individual to look like a more normal male or female.

In the case of a newborn infant, the choice of sex in rearing does not depend primarily on the genetic sex or on parental desires. The important consideration is whether this individual will be physically able to function in the role of male or female in later life. It is usually much easier to raise the intersex infant as a female than as a male, and in fact many are raised as females quite successfully, without the diagnosis ever being suspected. Minor abnormalities of the female external genitalia are often inconspicuous. Both as a child and as an adult, the female leads a less public existence than the male. It is surgically simpler to construct an artificial vagina from a urogenital sinus than to create a cosmetically satisfactory and functional penis. If a penile urethra is present, as for example in a true hermaphrodite, the problem is simplified. Such an individual probably should be raised as a male. In determining the sex of rearing, no consideration should be given to eventual fertility, since these persons are always sterile.

Once the decision is made as to the sex of rearing, it should be carried out systematically. Prolonged hesitation, which leaves the parents confused about the child's sex, is harmful to the emotional development of the child. The decision is made with full realization that the abnormal gonad may begin to secrete either androgens or estrogens at adolescence. The male pseudohermaphrodite successfully reared as a female may become virilized at puberty or, raised as a male, may develop breasts. One cannot be sure in advance what will happen. It is probably safe to wait until such changes begin and then remove the offending (sterile) gonads. At this later age, the internal genitalia can be corrected so as to conform to the sex of rearing.

It may seem arbitrary for the pediatric endocrinologist to decide that a genetic male should be reared as a female or vice versa, but the decision is based on experience gained from past errors in judgment. The physician will encounter no more tragic individual than one forced to assume a gender role for which "he" or "she" is physically completely unsuited, unless it be a child in whom a late attempt has been made to change his or her "sex." The future welfare of the child depends on an inner, unquestioned belief, largely gained from the parents, in turn supported by the physician, that he is a boy or that she is a girl.

Since the general practitioner usually sees these individuals in infancy, he is in a favorable position to direct them toward early diagnosis and treatment. Treatment can be started even before the patient is referred to a diagnostic center. The physician should reassure the parents that the developmental defect in the infant does not mean a sexual abnormality in the parents. He should tell them, whether they ask the question or not, that it does not imply psychosexual abnormalities in later life. He should suggest that the name chosen for the infant, which will appear on the birth certificate, be suitable for either a boy or a girl. It may be desirable for him to propose that the family settle in another area of the

same city, or even move to a neighboring town, if he suspects that there will be a great deal of emotional upheaval among the friends and relatives of the family. He should tell the parents that the "unfinished" genitalia can be made to look quite normal. Above all, appreciating the difficulty in diagnosing the true sex of the infant, the practitioner should emphasize to the parents the importance of early referral and treatment.

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MEETINGS and Postgraduate Courses

Academy of Psychosomatic Medicine, Chicago: Fourth annual meeting, October 17-19, at the Morrison Hotel. The program will cover the psychosomatic aspects of obstetrics, gynecology, endocrinology and diseases of metabolism. For further information, write to: Dr. William S. Kroger, Secretary, 104 South Michigan Avenue, Chicago 3.

American College of Chest Physicians: Postgraduate courses on diseases of the chest presented by the Council on Postgraduate Medical Education:

Hotel Knickerbocker, Chicago, October 21-25
Park-Sheraton Hotel, New York City, November 11-15
Ambassador Hotel, Los Angeles, December 9-13

For further information, write to: Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11.

American College of Surgeons, Atlantic City: 43rd annual clinical congress, October 14-18, at Convention Hall. The theme will be "Progress in Surgery as It Is Emerging From Research Laboratories and Operating Rooms." For further information, write to: Robert M. Cunningham, Public Relations Department, American College of Surgeons, 40 East Erie Street, Chicago 11.

New York University Post-Graduate Medical School, New York: Two week course on air pollution offered in cooperation with the New York University College of Engineering, December 2-13. For further information, write to: The Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16.

The New York Academy of Medicine, New York: Postgraduate Week, October 7-11. The program theme will be "Research Contributions to Clinical Practice." For further information, write to: Secretary, Postgraduate Week, The New York Academy of Medicine, 2 East 103rd Street, New York 29.

University of California Medical Center, Los Angeles: Symposium on current therapy in dermatology, October 25-27, sponsored by University Extension. For further information, write to: Dr. Thomas H. Sternberg, University of California Extension, Medical Center, Los Angeles 24, California.

University of Minnesota, Minneapolis: Courses to be presented at the Center for Continuation Study:

Obstetrics for general physicians, October 7-9
Symposium on skin cancer for specialists, October 24-26
Cardiovascular radiology for specialists, November 4-9
Physical medicine for specialists, November 18-20

For further information, write to: Director, Department of Continuation Medical Education, 1342 Mayo Memorial Building, University of Minnesota, Minneapolis 14.

University of Texas Postgraduate School of Medicine, Houston: Seminar on the current trends in gynecology, October 27-29. Guest lecturers will include Dr. Hans L. Kottmeier of the Radiumhemmet, Stockholm, Sweden. For further information, write to: Dean of The University of Texas Postgraduate School of Medicine, 410 Jesse Jones Library Building, Houston 25.

Congenital Disorders of Renal Tubular Function

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A MAJOR function of the kidneys is the regulation of the volume and composition of the body fluids so that a relatively constant environment is maintained for the functioning of the cells. This is achieved by the modification of the glomerular filtrate as it passes through the tubules with differential reabsorption of water and solutes from the tubular contents and secretion of other solutes into the urine. Many separate tubular mechanisms are involved in this complex function, and it is not surprising that a variety of inborn errors of metabolism exist in which certain of these mechanisms are defective. These defects are of biochemical systems. They are not necessarily correlated with any demonstrable anatomic abnormality of the kidneys, but result in specific metabolic disturbances. In some instances, the renal handling of only a single substance is altered; in other instances, a more complex disorder results since the reabsorption or secretion of a group of interrelated solutes is involved. This discussion will be concerned with several of the clinical syndromes associated with congenital anomalies of tubular function.

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Nephrogenic Diabetes Insipidus

In this condition, the defective tubular mechanism is that required for the formation of a concentrated urine; i.e., the system for reabsorption of water in the distal portion of the tubule which is normally controlled by the antidiuretic hormone of the posterior pituitary. There is no lack of antidiuretic hormone, but rather failure of response of the renal tubule. This abnormality is transmitted as a sex-linked recessive character. The full-blown disorder occurs only in males, but is transmitted through the females. Although the female carrier is grossly normal, it has been shown that a mild limitation of concentrating ability is present in the mothers of infants with nephrogenic diabetes insipidus.[1]

The affected infants have polyuria and are unable to tolerate water restriction from birth on. Since the presence of polyuria may not be appreciated in young infants, the diagnosis may not be made except as manifestations of

water loss are noted. The affected infants are irritable, grow poorly and fail to gain weight. Constipation and excretion of dry desiccated stools commonly occur. Irregular temperature elevations may result from dehydration, and acute episodes of severe water deficit are seen if infection causes anorexia or vomiting. These episodes are characterized by marked weight loss, fever and extreme listlessness. The infants continue to excrete a dilute urine until markedly dehydrated.

The characteristic biochemical change is hyperelectrolytemia; i.e., loss of water in excess of electrolyte so that the concentrations of sodium and chloride in the serum are elevated. In the stage of severe dehydration, reduction of the glomerular filtration rate occurs with oliguria and rapid rise of blood urea nitrogen. In the well-hydrated state, the glomerular filtration rate is normal, as are the results of other tests of kidney function except for the failure of excretion of a concentrated urine following PITRESSIN® injection or water restriction. Retardation of mental development sometimes has been associated with this syndrome, but it is not necessarily present. It has been suggested that cerebral injury may result from recurrent or persistent hypernatremia, since there is evidence that acute hypernatremic dehydration in otherwise normal infants can cause cerebral damage.[2]

Nephrogenic diabetes insipidus is distinguished from true diabetes insipidus by failure of response to Pitressin injection. If large doses of Pitressin are given in an effort to produce antidiuresis, the vasomotor effects and spasm of the intestinal smooth muscle due to Pitressin occur without any antidiuretic effect.

The period of infancy is usually stormy owing to the difficulty in achieving adequate water intake complicated by acute dehydration during intercurrent infections. During this period, weight gain and growth are poor. As the infants grow older, sufficient water, up to 5 or 6 l. a day, can be taken, and improvement in growth and development is noted. It is possible for these patients to reach adult life but there is never any improvement in the defect of water reabsorption by renal tubules.[3]

Renal Glycosuria

This is another example of an isolated defect of renal tubular function. In this instance, there is inadequate tubular reabsorption of glucose from the glomerular filtrate, and as a result glucose is found in the urine when its concentration in the plasma is normal. This is probably a hereditary abnormality since the manifestations have been found in early childhood and a familial incidence has been reported. Inasmuch as the defect does not produce any serious physiologic disturbance, it may go undiagnosed and may be discovered only on routine urine examination. The pattern of inheritance has not been clearly established, and there may be several types of renal glycosuria in terms of heredity and specific tubular defect. Physiologic studies have indicated that in some patients the maximal capacity of the tubules to reabsorb glucose, T_{mG}, is reduced, indicating a biochemical deficiency of all of the tubules, whereas in others the T_{mG} following loading with glucose is in the normal range, even though glucose appears in urine at low concentrations of glucose in plasma. It has been suggested that in this latter type there is marked variation of tubular capacity to reabsorb glucose and impairment of reabsorption in some tubules but normal tubular reabsorptive capacity in others.[4]

Renal Glycosuria and Amino-aciduria

This syndrome has been described only recently, and possibly some of the reported cases of renal glycosuria may actually belong to this group. The amino-aciduria is generalized, and all of the amino acids occurring in plasma are excreted in the urine in excessive quantities. The disorder of amino acid reabsorption is similar to that seen in the Fanconi syndrome (*vide infra*), but the patients have no obvious physiologic disturbance aside from the urinary abnormalities. This defect has been observed in a set of twins, their father and possibly the paternal grandfather, so that it is presumably inherited as a dominant character.[5] I have studied a young woman who has this combination of renal glycosuria and amino-aciduria. Incomplete studies have not revealed any other

cases of a similar disorder in this family. The glycosuria was first known to be present in this patient when she was 10 years of age, and the amount of glucose excreted was greater than in most cases of renal glycosuria. Her presenting complaints of vulvovaginitis with severe pruritus were presumably due to the intense glycosuria. Physiologic studies following glucose loading revealed a marked reduction of T_{mG}. Amino acids were determined and identified in the urine by the technic of paper chromatography, and she was found to have a generalized amino-aciduria similar to that seen in the Fanconi syndrome. She had no disturbance of phosphate metabolism or osteomalacia. No apparent clinical manifestations could be ascribed to the amino-aciduria. It may be, however, that studies of amino acid excretion in renal glycosuria may be of value in the differentiation of various types of this disorder.

Essential Renal Cystinuria

This is a hereditary renal tubular defect of reabsorption of cystine, lysine, arginine and ornithine. These four amino acids appear in the urine in excessive amounts, but until recent years only cystine was identified in the urine. Cystine is relatively insoluble in the physiologic pH range so that it crystallizes in urine if present in high concentration and forms aggregates of cystine crystals and cystine calculi. Studies of the urine of cystinuric patients by chromatographic methods have revealed that the basic amino acids lysine, arginine and ornithine are also present in addition to cystine, and, inasmuch as the plasma concentrations of these amino acids are not increased, the biochemical defect is localized in the renal tubules.

According to Harris and associates,[6] there may be two hereditary patterns in cystinuria. In one, the transmission is by a recessive gene and the manifestations are found only in the homozygous state, whereas the heterozygous parents of affected children do not have any demonstrable abnormality of urinary excretion of these four amino acids. In the second variety, the genetic pattern suggests an incompletely recessive gene, and a partial abnormality is found in the heterozygous individuals and results in moderate increase of cystine and lysine in the urine. The clinical manifestations are only those of precipitation of cystine calculi, and the two hereditary patterns cannot be separated on clinical grounds. Since cystine calculi do not form in all cases of cystinuria, the incidence is greater than indicated by the relatively rare occurrence of cystine stones. The formation of cystine stones can be minimized by administration of alkalinizing salts since cystine is more soluble in alkaline urine.

The congenital defects thus far discussed involve disturbances of isolated functions of renal tubules. Although the defect of water reabsorption in nephrogenic diabetes insipidus can lead to serious physiologic disturbances if water intake is inadequate, the hydrated patients do not have any metabolic abnormality except for polyuria. The impairment of glucose reabsorption or even amino acid reabsorption may also have no major physiologic consequences. There are, however, more complex disturbances of renal tubular functions associated with serious metabolic disorders of clinical significance. Most interesting, perhaps, are those in which impairment of renal tubular reabsorption of phosphate occurs. This dysfunction results in hypophosphatemia and rickets or osteomalacia caused by phosphate deficiency.

Cystine Storage Disease or Cystinosis

This is one of the syndromes in which renal tubular reabsorption of phosphate is deranged along with other tubular functions, and hypophosphatemic rickets occurs. This is a rare and grave metabolic disorder, and must be distinguished from renal cystinuria which is a comparatively benign error of tubular metabolism. Cystinosis is familial, and the inheritance is that of a recessive gene with multiple instances in siblings but without detectable abnormalities in the parents.[7] The basic metabolic defect is still unsolved, but one of the primary manifestations is accumulation of cystine crystals in large phagocytic cells in the reticuloendothelial tissue throughout the body. The renal tubular disturbances are but one facet of the generalized metabolic disorder, and are in themselves complex. There is im-

pairment of renal tubular reabsorption of glucose, amino acids and phosphate. In addition, there may be abnormalities of tubular function with respect to the regulation of acid-base balance and potassium excretion so that metabolic acidosis and hypokalemia result. The abnormality of phosphate reabsorption results in phosphate deficit and hypophosphatemia which, in turn, causes the defect of salt deposition in bones, which is clinically recognizable as rickets and osteomalacia.

The affected infants appear to be normal at birth, and may show no untoward effects during the first few months of life. Growth then begins to lag, and the usual presenting complaints are failure to thrive, poor weight gain, slow growth, muscle weakness and lassitude. In other cases, retardation of growth may be less striking, and skeletal deformities of rickets may appear at about a year or so of age. Even in the infants with poor growth, evidences of rickets can be found by x-ray examination of the long bones. The urine contains detectable amounts of glucose and an excessive amount of amino acids. The latter can be determined and the individual amino acids identified by the technic of paper chromatography. It has been shown that all of the amino acids normally present in plasma are excreted in the urine in increased amounts, and that the concentration of amino acids in plasma is not increased despite the presence of cystine in the tissues. The amino-aciduria is, therefore, renal in type owing to impairment of renal tubular mechanisms. The diagnosis is confirmed by biopsy of bone marrow or lymph nodes and by the demonstration of cystine crystals in the smears. Cystine crystals also are deposited in the cornea, and they can be detected by slit lamp microscopy.

The patients can be treated by the daily administration of 25,000 to 50,000 units of vitamin D. This will increase phosphate retention, elevate the concentration of serum phosphorus and cause healing of the rachitic and osteomalacic lesions in the bone. Apparent improvement of renal tubular function and diminution of the glycosuria and amino-aciduria also have been reported to result from vitamin D therapy. Feeding of sodium and potassium citrate mixtures may also be of benefit, especially in those children with metabolic acidosis. The fundamental biochemical anomaly is not corrected, however, progressive liver and renal injury and fibrosis usually develop, and renal insufficiency ultimately results. As in any chronically ill child, secondary infection may be of importance as a terminal event.

The triad of renal glycosuria, renal amino-aciduria and renal phosphaturia associated with hypophosphatemic rickets and osteomalacia is usually referred to as the Fanconi syndrome. In infancy, cystinosis is the most important cause of the Fanconi syndrome, but this disorder of renal tubular function can be found in older children and adults without evidence of cystine deposition in tissues. The Fanconi syndrome in the older age group is probably a heterogenous group of disorders due to multiple causes. In some cases, a familial occurrence has been found, and suggests a hereditary disorder other than cystinosis. In other cases, no apparent familial incidence has been found, and the possibility exists that the tubular defect might be an acquired injury. It is known that heavy metals, acids and other toxic agents can produce renal tubular injury which results in renal glycosuria, amino-aciduria and even phosphaturia.[8] The prognosis of the Fanconi syndrome without cystinosis is probably better than that of cystine storage disease. Treatment with vitamin D and, in some instances, with sodium potassium citrate will produce healing of the disorders of skeletal calcification, which is the most important manifestation of the Fanconi syndrome in older children and adults. Such complications as hepatic cirrhosis and scarring of the kidneys do not occur in this syndrome as they do in cystinosis.

Congenital Renal Tubular Acidosis

The tubular dysfunction in this syndrome is believed to be a failure of the mechanism for the formation of acid urine by exchange of the H^+ ion of the tubular cells for the cations Na^+, K^+, Ca^{++} and Mg^{++} in the tubular contents. The urine excreted is neutral or alkaline even though the diet provides an excess of acid over base. Consequently, a metabolic aci-

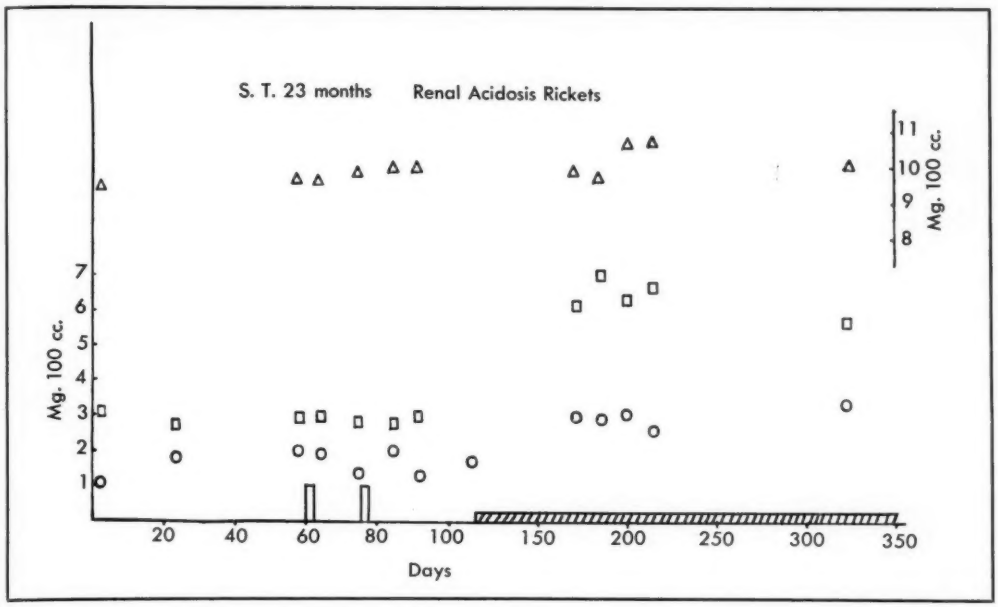

FIGURE 1. Effect of vitamin D and of feeding sodium lactate on concentrations of calcium, phosphorus and citrate in serum of a child with congenital renal tubular acidosis and hypophosphatemic rickets. △, Calcium, mg. per 100 cc.; □, phosphorus, mg. per 100 cc.; o, citrate, mg. per 100 cc.

The two hollow columns indicate the administration of vitamin D in doses of 600,000 units. The diagonal hatched zone indicates the period during which 40 cc. of a molar solution of sodium lactate was administered daily in divided doses. Note the failure of response of the serum phosphate and serum citrate to the administration of vitamin D during the period in which the acidosis was not treated. After correction of the acidosis with sodium lactate solution, the concentrations of serum phosphate and serum citrate increased to normal, and roentgenographic examination revealed healing of the rickets.

dosis develops and is manifested by a reduction of serum bicarbonate concentration and a reciprocal elevation of the concentration of serum chloride. This combination of hyperchloremic acidosis and excretion of a neutral or alkaline urine is the important diagnostic feature of renal tubular acidosis. In addition, there is impairment of tubular reabsorption of phosphate which may be secondary to the acidosis. The combination of metabolic acidosis and hypophosphatemia results in retardation of growth and the skeletal changes of rickets. A disturbance of tubular reabsorption of water is also characteristically seen in the affected children, and polyuria is one of the initial manifestations. The failure of concentration of urine is not as marked, however, as in nephrogenic diabetes insipidus. Although this metabolic disorder is presumably congenital, since the manifestations are noted in early infancy, its inheritance is not clearly established. Although this disorder has been reported to have occurred in a few siblings, no familial incidence has been apparent in any other cases.

The earliest clinical manifestations are growth retardation, lack of weight gain and polyuria. If no definitive treatment is given, the skeletal changes of rickets appear by the end of the first year of life, and severe skeletal deformities may develop. The administration of vitamin D even in fairly large doses does not cause healing of the rickets unless the metabolic acidosis is corrected. This can be done by feeding a large excess of base such as sodium bicarbonate or the sodium salts of a metabolizable organic acid such as lactate, citrate or acetate. Since excess loss of potas-

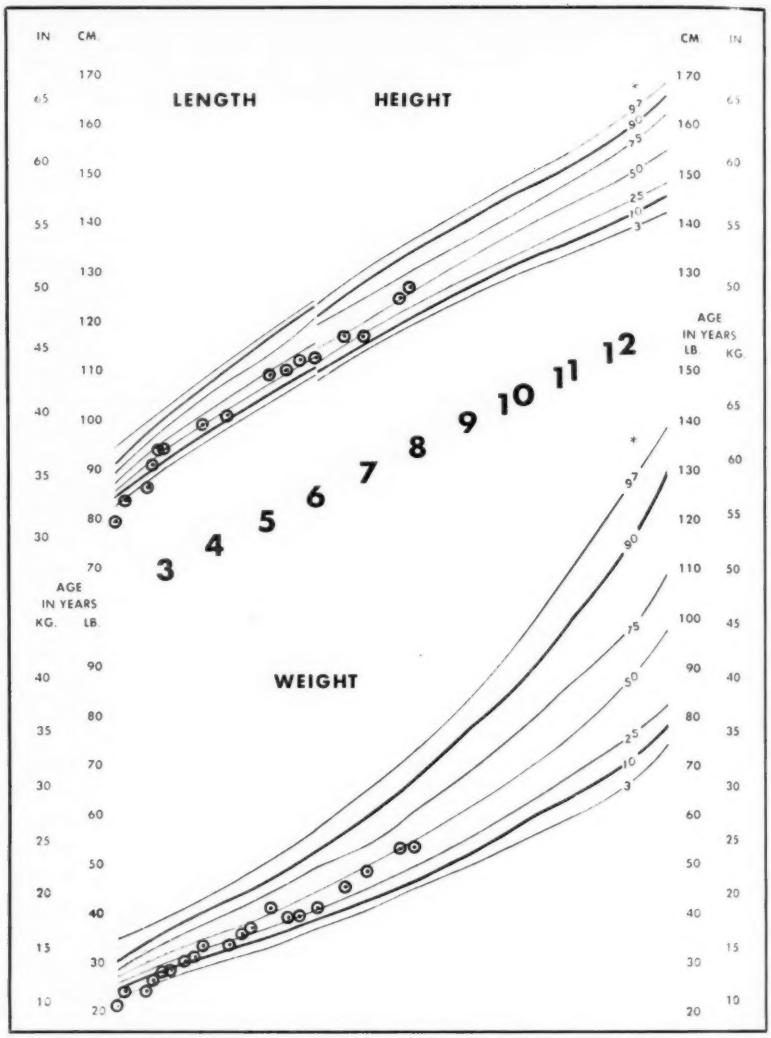

FIGURE 2. Growth curves of children with renal tubular acidosis.
a. Diagnosis of renal tubular acidosis was made when the child was 23 months old. Rickets was severe. Daily administration of 40 cc. of a molar solution of sodium lactate in milk corrected the acidosis. In addition, 50,000 units of vitamin D was administered daily, although this probably was more than was necessary. The height and weight curves indicate the restoration of normal growth, which has been maintained for more than six years. Nephrocalcinosis has not developed.

sium may occur in renal tubular acidosis as in the Fanconi syndrome, a mixture of sodium and potassium salts may be theoretically indicated, and we have used for this purpose a sodium and potassium citrate solution which can readily be given to children. The composition of the solution is as follows:

Citric acid	66 gm.
Sodium citrate	100 gm.
Potassium citrate	110 gm.
Fruit-flavored syrup to make	1000 cc.

One cubic centimeter of this solution contains 1 mEq. of sodium and 1 mEq. of potassium. The daily administration of 30 to 40 cc. of this solution or comparable amounts of a molar solution of sodium lactate has effectively restored to normal the serum bicarbonate and chloride concentrations of children with renal tubular acidosis. Correction of the acidosis is associated with more normal renal tubular reabsorption of phosphate, so that there is increased phosphate retention, elevation of serum phosphorus levels, and increased

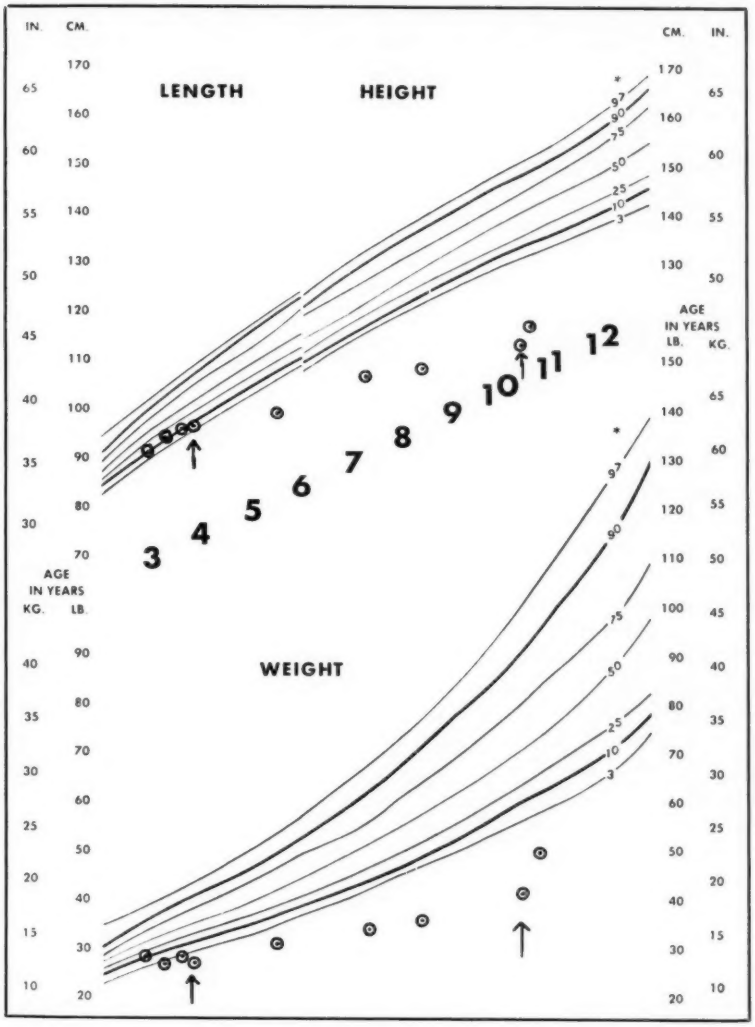

FIGURE 2b. Diagnosis of renal tubular acidosis was made when the child was three months old. Daily administration of a solution of sodium lactate and 5000 units of vitamin D produced relatively good healing of rickets and adequate growth despite roentgenographic evidence of nephrocalcinosis. When the child was between three and four years of age (indicated by first arrow), treatment was neglected. As a result, growth was retarded, low-grade rickets recurred, and bowing of the femurs developed. When the child was 10 years old (indicated by second arrow), administration of a molar solution of sodium-potassium citrate was begun, and better cooperation was obtained. Healing of the rickets occurred, and a suggestive increased spurt of growth was achieved. The daily dose of vitamin D was maintained at 1000 units.

deposition of calcium and phosphate in the skeleton with healing of the rickets.

The considerable urinary loss of calcium which is seen during the acidotic state is reduced by treatment of the acidosis. Figure 1 indicates the effect of sodium lactate on the serum calcium and serum phosphorus of a child with renal tubular acidosis and severe rickets who had failed to respond to large doses of vitamin D. Treatment of the acidosis also results in restoration of normal growth as is shown in figure 2a. The fundamental tubular defect is not healed, however, by administration of excess cation. Polyuria persists and the acidosis recurs if the alkalinizing regimen is stopped. With inadequate treatment, a relapse occurs in the retardation of growth and in the rachitic changes (figure 2b).

One of the important complications of renal tubular acidosis is renal calcinosis in which the calcium deposits are concentrated in the medulla and pyramids of the kidneys. Intratubular precipitation of calcium salts is thought to occur because of their insolubility in

TABLE 1

CONGENITAL DISORDERS OF RENAL TUBULAR FUNCTION: SUMMARY OF SPECIFIC RENAL TUBULAR SYSTEMS INVOLVED IN THE VARIOUS SYNDROMES

SYNDROME	WATER REABSORPTION	GLUCOSE REABSORPTION	AMINO ACID REABSORPTION	PHOSPHATE REABSORPTION	H ION EXCHANGE	K ION EXCHANGE
Nephrogenic diabetes insipidus	+	−	−	−	−	−
Renal glycosuria	−	+	−	−	−	−
Renal glycosuria and amino-aciduria	−	+	+	−	−	−
Essential cystinuria	−	−	+*	−	−	−
Cystinosis (Fanconi's syndrome)	−	+	+	+	±	±
Renal tubular acidosis	+	−	−	+	+	±

*Defect of reabsorption of cystine, lysine, arginine and ornithine, but not of other amino acids.

alkaline urine. A disorder of renal citrate metabolism which has been found in cases of this disorder may also be a factor.[9] In normal persons, alkalinization of the urine is associated with an increase in citrate output which may be important in increasing the solubility of calcium salts. In renal tubular acidosis, the urine is extremely low in citrate despite the alkaline reaction. Although roentgenologic examination may disclose the presence of renal calcinosis, adequate treatment of the acidosis may prevent the progress of the process, perhaps by reducing the excretion of calcium in the urine. The ultimate prognosis of this disease in cases in which the patients are treated early cannot be predicted at present.

Lightwood, Payne and Black[10] have described a clinical syndrome which resembles congenital renal tubular acidosis and which occurs in infants. Complete recovery apparently occurs in cases of this syndrome. Failure to thrive and poor weight gain are the initial symptoms. Laboratory studies show a hyperchloremic acidosis and a neutral or alkaline urine. The affected infants improve following administration of alkalinizing salts, and eventually recover completely so that treatment can be discontinued. A defect of tubular function which is corrected in the course of growth and maturation has been suggested as the basis of this disorder.

Summary

In some congenital disorders of renal tubular function, only one function is impaired; in others, the disturbance is more complex, and interrelated functions are involved. Table 1 shows the different functions that are altered in the particular syndrome. Some of these inborn errors of renal tubular function are not associated with any generalized metabolic disorder and are diagnosed only by the discovery of abnormal amounts of certain substances in the urine. Other tubular defects result in profound changes in the composition of extracellular fluids which are responsible for serious functional disturbances. It is likely that other renal tubular defects of genetic origin will be recognized as new technics are applied to studies of a large number of patients.

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Bleeding From the Anus in Children

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PARENTS are always alarmed by the passage of blood from a child's anus. The physician, realizing that in a majority of cases anal bleeding is relatively harmless, is often led into prematurely reassuring the worried parents before ruling out the less common serious conditions in which blood in the stool may be the first sign. On the other hand, the same worried parents may so exaggerate the findings as to lead the physician into unnecessary diagnostic or therapeutic procedures. In any event, in the interest of our reputation as diagnosticians, as well as for the prompt and proper management of the case, it is worthwhile to clarify the differential findings of the causes of a condition that is so fraught with diagnostic pitfalls.

In reported cases of bleeding from the anus in children, there is a wide variation in the causes of this condition and in their relative frequency. In 26 per cent of 228 cases reported by Baffes and Potts,[1] the bleeding was due to intussusception. Other frequent causes included enterocolitis (15 per cent), anal fissure (11 per cent), Meckel's diverticulum (10 per cent), and polyps (7 per cent). No other condition was responsible for the bleeding in as many as 5 per cent of the cases. Kiesewetter, Cancelmo and Koop[2] listed 20 conditions which may cause rectal bleeding in infants and children, and said that fistula in ano is the most frequent cause. Mentzer[3] reported the results of a study of 147 cases in which anorectal disease occurred in children. The most frequent disease was anal fistula, which was present in 32 per cent of the cases. Other frequent diseases included prolapse or procidentia, abscess and fistula, and polyps, in that order. No other disease was present in as many as 5 per cent of the cases. Bleeding usually is a prominent symptom of all of these diseases.

The cases reported by these and other authors are cases in which the patients have been observed in the departments of surgery or proctology of hospitals. They, therefore, are a selected group of cases. I do not know of any

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TABLE 1

SIGNS AND SYMPTOMS OF BLEEDING FROM THE ANUS IN CHILDREN

CAUSE	AGE AND SEX	BLOOD				PAIN	ASSOCIATED SIGNS AND SYMPTOMS
		Color	*Amount*	*Relation to Stool*	*Relation to Defecation*		
Anal fissures, abrasions, erosions and ulcers	Less than 2 yr.	Bright red	Small	Streaked on stool	During or after defecation	Severe	Blood visible on spreading anus
Enterocolitis (all types)	Any age; most common in infants	Bright to dark red	Small	Streaked on and mixed in stool	During defecation (intermittent)	Cramps	Diarrhea; pus and mucus in stool; findings characteristic of the specific type
Polyps (three types)	2 to 5 yr.	Bright if from rectum; darker if from small intestine	Small or large; may be occult	Streaked on and mixed in stool	During defecation, but may be after	Unusual	Persistent anemia and malnutrition; recurring intussusception; malignant disease (polyposis); vague abdominal pain
Meckel's diverticulum	Any age; girls (3:1)	Brick red	Massive in episodes; small if intermittent	Streaked on or mixed in stool	With or without defecation	None with bleeding	Signs of acute or chronic hemorrhage
Intussusception	Under 2 yr.; more common in boys	"Currant jelly"; dark later	Small	Mixed in stool	During and after defecation	Severe colic	Sudden onset; shock and vomiting; abdominal mass
Rectal prolapse and procidentia	1 to 3 yr.	Bright; mixed with mucus	Small	On stool	During or without defecation	Straining cramps	May be constipation; malnutrition; celiac syndrome
Lesion of upper part of gastrointestinal tract	Any age	Tarry; may be bright red in young infants	Small or large	Mixed in stool	During defecation	None with passage	Signs of etiologic disease
Systemic disease	Any age	Bright red to tarry	Small or large	Mixed in stool	During defecation	None with passage	Signs of etiologic disease

report of a similar group of cases in which the patients have been observed in the office of a pediatrician or general practitioner. As a result of many years of observation, my impression, which is supported by a number of my colleagues, is that anal erosion, ulcer and fissure are responsible for most instances of anal bleeding in children. Other common causes are enterocolitis, polyps, Meckel's diverticulum, intussusception and prolapse or procidentia, but not necessarily in that order. Other conditions that may cause such bleeding are uncommon, and cause signs and symptoms which are more prominent and important than the anal bleeding.

A start toward an accurate differentiation of the causes of bleeding can be made by close attention to the character of the blood and of the bleeding (table 1). In general, dark changed blood comes from high in the gastrointestinal tract, bright red blood from lower down. Blood streaked on the outside of the stool usually comes from the rectum or anus, whereas blood mixed with the stool comes from the proximal part of the large bowel. The blood in tarry stools most often comes from the upper part of the gastrointestinal tract. Profuse bleeding more often points to a surgical lesion.

It is important that the physician examine the stool rather than rely on a description by the parent, whose evaluation of the amount or color of the blood or of its relation to the stool is notoriously inaccurate.

Anal Abrasions, Erosions, Fissures and Ulcers

These are undoubtedly the commonest causes of anal bleeding seen in pediatric practice. They have a common origin, and on superficial examination they all look much alike. They are the result of trauma, most frequently from the passage of a hard stool or a stool of large diameter. The inexpert use of a rectal thermometer or of a suppository is also a frequent cause. Anal stenosis, especially the commonly seen anorectal ring of the newborn,[4] is often a predisposing cause. Irritation from scratching due to perianal eczema or intestinal parasites can occasionally be a factor. Abrasions, erosions, fissures and ulcers occur most commonly in infants and are rarely seen in children more than two years of age. The presenting symptoms are severe pain on defecation, and bright blood streaked on the stool or after the stool, or both. Because of the pain, the infant holds back the passage, which aggravates the constipation and starts a vicious cycle. Most of these lesions can be seen by digitally spreading the anus. This is probably unfortunate, since it makes ill-advised topical applications too easy. The lesions are usually shallow, single or multiple erosions or abrasions involving the superficial layers of the mucosa. Rarely do untreated lesions extend to or into the muscularis. They occasionally are associated with cryptitis. They respond to careful dilatation with a well-oiled gloved finger, a diet designed to correct constipation, and the use of a methylcellulose preparation to produce a soft bulky stool.[5] A retention enema including an antiseptic and an analgesic is helpful in avoiding pain on bowel movement. It also is valuable in the prevention or treatment of the frequently associated cryptitis.*

Practically all acute fissures yield promptly to conservative treatment. Topical applications, especially of silver nitrate, are not indicated. The use of any cauterizing or astringent agent is not only unnecessary and very painful to the child, but it often converts a superficial abrasion into a deep fissure, ulcer or abscess, and ultimately into a chronic lesion requiring surgical treatment.

Enterocolitis

Enterocolitis of all types constitutes the second most common cause of bleeding from the anus. This group includes the specific enteritides, epidemic diarrhea both of the new-

*Benzocaine	32 gr.	(2.0 gm.)
PROTARGOL®	2½ gr.	(0.16 gm.)
Lanolin	1½ drams	(6.0 gm.)
Glycerin	1½ drams	(6.0 gm.)
Liquid petrolatum q.s. ad	1 oz.	(30.0 cc.)

Add 1 oz. of mineral oil to 1 teaspoonful of the mixture and inject, at body temperature, with a bulb syringe once a day at the usual time of the bowel movement.

If pain on defecation is severe, 32 gr. of BUTYN® sulfate can be used in place of the 32 gr. of benzocaine. The mixture should be well triturated.

FIGURE 1. Solitary polyp in the sigmoid.

born and of older infants, allergic intestinal reactions, amebic dysentery, ulcerative colitis and chronic regional enteritis. In most cases, diarrhea rather than bleeding is the prominent presenting symptom. Here again, the diagnosis is apparent from a careful history, and by repeated examinations of the stool. A description of the stool by the mother is a poor substitute for looking at the stool. Blood is only intermittently present, scanty, and usually not intimately mixed with the stool. The bowel movements are frequent, unformed, and often watery green or yellow in color, and contain mucus or pus. They are often explosive in their passage and may be accompanied by pain. Enterocolitis with bleeding from the bowel, which requires intensive medical management, can be confused with a simple parenteral diarrhea associated with proctitis and bleeding from anal erosions. This condition calls for more simple treatment. Here again, the differential diagnosis is simple if the physician examines both the anus and the stool.

Polyps

There are three general types of polypoid disease of the intestine in children: (1) single or multiple polyps in the large bowel; (2) multiple polyps in the large and small bowel, and (3) multiple polyposis.

Single or multiple polyps in the large bowel—This is the most common type of polypoid disease, and is most easily diagnosed. David[6] says that this disease is the most common cause of rectal bleeding in children who are between two and five years of age. The blood is bright red, usually on the outside of the stool, but occasionally mixed in it. The blood may accompany the stool in small or large amounts, or it may follow defecation. Continued urgency and straining after stool are common. Rectal polyps can usually be identified and removed through the proctoscope. Polyps beyond the range of the proctoscope are identified by roentgenographic examination following a barium enema (figure 1). Their removal calls for colotomy.

Multiple polyps of the large and small bowel—In this type of polypoid disease, bleeding may be absent for long periods. When it occurs, the blood is mixed with the stool and is darker in color except in the uncommon cases in which the polyp is low in the colon. The symptoms then are those of the first type. Only occult blood may be present, and there may be no history of bleeding from the rectum at any time. Often more prominent symptoms are listlessness, irritability, failure to gain weight, pallor, and a persistent hypochronic, microcytic anemia. Persistent or recurring anemia in a child calls for a search for gross or occult blood in the stool. The most common cause of chronic loss of apparent or occult blood from the bowel is the presence of one or more polyps in the small or large intestine. Intussusception may be the presenting symptom. Polypoid disease must always be considered as the cause of an intussusception, especially if the intussusception is recurrent. An interesting sign occasionally seen in this type is the presence of brown

melanin spots on the child's lips or oral mucosa (figure 2). This combination of findings, referred to as the Peutz-Jeghers syndrome,[7] has a familial incidence. Occasionally, a brilliant diagnosis is the reward of the thorough clinician who observes these spots. The polyps are identified and localized by a barium enema, or a postevacuation enema (Fischer procedure) prior to their surgical removal. The chance of the development of new polyps must be kept in mind.

Multiple polyposis—This is a familial disease characterized by the presence of many, sometimes hundreds of polyps distributed throughout the large bowel. They are more prone to malignant degeneration than the other two types. Rectal bleeding is intermittent. The blood passed is usually bright red, small in amount, mixed with the stool or streaked on it, and not associated with pain. The diagnosis is readily made by proctoscopic and roentgenographic examination. Because of the marked tendency to malignant degeneration, the question of colectomy must be seriously considered, and evaluated in each case individually.[8]

Meckel's Diverticulum and Reduplication of the Bowel

The bleeding from Meckel's diverticulum or persistent omphalomesenteric duct characteristically is the sudden painless passage of massive amounts of dark red clotted blood. Often the classic symptoms of acute hemorrhage and shock are present. This was the clinical picture in 85 per cent of the 27 cases in which the patients were treated at Children's Memorial Hospital in a period of six years.[1] In the other cases, smaller quantities of blood from bright red to dark in color were passed at intervals of months to years. The bleeding is almost always secondary to digestion of the intestinal mucosa by the secretion of aberrant gastric or pancreatic glands in the diverticulum. The condition may occur at any age from birth through childhood. Because of the occurrence of gastric and pancreatic tissue in reduplicated bowel, a similar picture may occur in this less common anomaly. If the hemorrhage can be controlled by multiple transfusions, the diverticulum or reduplicated bowel is removed after bleeding has ceased.

FIGURE 2. Melanin spots associated with polypoid disease.

If hemorrhage continues, an emergency laparotomy is mandatory.

Intussusception

In contrast to Meckel's diverticulum, bleeding in cases of intussusception is a confirmatory rather than a presenting symptom. Here the picture is that of sudden intermittent colicky pain and vomiting in a child under two years of age. There are rapidly increasing prostration and shock. A doughy, sausage-shaped tumor mass is palpable somewhere along the course of the colon. Anal blood is usually not noted in the first few hours. It often is seen first on withdrawal of the examining finger from the rectum, and it is characteristically mixed with mucus—the classic currant-jelly stool. The clinical picture is remarkably constant, and is so characteristic that a barium enema, which is not without danger, is not necessary for diagnosis. Instead, immediate surgical exposure and manual reduction have many advantages. They are the safest method of reduction, and permit the examination for and correction of any predisposing cause which may be present, such as Meckel's diverticulum, a polyp or other intestinal tumor, or a foreign body. There is a further justification for laparotomy. The two conditions most easily confused with intussusception are volvulus and mesenteric thrombosis. Exploratory laparotomy is sometimes necessary for a differential diagnosis, and of course is essential in the treatment.

Rectal Prolapse and Rectal Procidentia

These are not common and do not always cause bleeding. They are rare in children more than three years of age. They are seen in malnourished children, particularly in children with celiac syndrome, in chronic constipation, or in persistent anorectal ring with straining at stool. In prolapse, there is an abnormal descent of the rectal mucosa. In procidentia, all of the coats of the rectum or the sigmoid or both descend. In either condition, there may be protrusion from the rectum, but not necessarily so. Bleeding, when it occurs, consists of bright blood mixed with mucus, expelled without stool or on the outside of the stool. The diagnosis is apparent when there is protrusion from the anus. If the mass does not protrude, the proctoscope readily clarifies the diagnosis. Conservative treatment, directed at diet and nutrition, together with strapping the buttocks are effective in most cases.

Blood Coming From the Upper Part of the Gastrointestinal Tract

In most cases the presence of blood in the stool is a secondary symptom. The etiologic conditions include bleeding from the mouth and nose, hemoptysis, maternal blood ingested at birth, blood swallowed by a nursing infant from a bleeding nipple, esophageal varices, duodenal or gastric ulcer, and, rarely, an ingested foreign body. Occasionally, these conditions may be silent, and the presence of blood in the stools may be the presenting symptom. Ordinarily, blood descending from the stomach is black and tarry when passed, but Apt[9] has shown that as little as 10 cc. of ingested blood can appear as red blood in the stools of newborn infants past the meconium period.

Systemic Disease

Occasionally, the initial sign of purpura, hypoprothrombinemia, leukemia and other blood dyscrasias is a bloody stool. In almost any chronic debilitating or deficiency disease, there may be episodes of rectal bleeding. Although the cause can usually be identified by its more characteristic symptoms, the possibility of systemic disease must always be kept in mind in rectal bleeding of obscure origin.

Bleeding of Undetermined Origin

It is personally comforting to find in a number of published series an item listed as "negative findings" or "undiagnosed melena." This type of bleeding constitutes between 10 and 15 per cent of the total cases of bleeding in these series. In most of the cases in which the cause of the bleeding was undiagnosed, the bleeding occurred in the neonatal period. In some of these it may be due to swallowed blood during delivery. Apt and Downey[10] have suggested the identification of fetal hemo-

globin in the anal blood as a means of determining whether the blood has come from the mother or the infant. Recurrent sigmoidal intussusception, described by Kiesewetter et al.,[2] may explain the bleeding in some cases in which the patients are older infants. They found this condition in 18 of a series of 143 cases of rectal bleeding. They stated that the presence of the condition is missed unless an adult-sized proctoscope is used.

Fecal Substances Which Resemble Blood

Substances which impart a red or black color to the stool are usually only conversation pieces, but occasionally they lead to a wrong diagnosis and unnecessary treatment. Such substances are beets, tomatoes, prunes and grape juice, especially if taken in large amounts and not mixed with other foods. The first two substances can cause a red stool; the last two, a black stool. Other substances which occasionally find their way into the feces include red or black crayons, MERCUROCHROME® used in the child's nose or throat, and the coloring matter used in some candies. A pink color can be imparted to the stool and to the diaper by uric acid in the urine. These are the source of many a frantic phone call. Few physicians will be misled by these artefacts if they personally examine the stool specimen, but a description by a parent can be very misleading.

There is another error into which physicians may fall if they rely on the parent's description of a bleeding episode. It is known that a teaspoon of blood can turn the water in the toilet bowl a bright red color, but to the parent it looks like, and is described as, an exsanguinating hemorrhage.

The first diagnostic procedure, then, should be an on-the-spot examination of the stool in which there is "blood." The characteristics of the stool can be preserved for several hours by putting it—including the diaper, in the case of an infant—in an airtight MASON® jar. This simple procedure will often convert a potential emergency situation into a routine office call.

Summary

Bleeding from the anus is a common finding in infants and children. In the majority of cases, the cause is simple, but in some the underlying condition is serious, and may be emergent. The more common causes have been discussed, and an attempt has been made to base a differential diagnosis on the following criteria: the age of the child, the color and amount of blood that is passed, the relation of bleeding to the stool and to defecation. and the associated signs and symptoms. The danger of cauterizing fissures, which are the most common cause of anal bleeding, has been stressed. Finally, it is my opinion that the most important single task of the physician in the management of bleeding from the anus is a careful examination of the anus and of the stools.

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The Causes of Vomiting in Infancy and Childhood

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In infancy and childhood, more than in any other age group, causes of vomiting are numerous and varied, differential diagnosis is more often difficult, disturbances of fluid and electrolyte balance are more sudden and severe, and undesirable complications develop more frequently and are more important.

Although vomiting is sometimes transient and trivial, it is frequently protracted and severe. It often leads to such ill effects as extensive alterations in fluid and electrolyte balance, impairment of renal function, ketosis, destruction of tissue through starvation, failure to gain weight or frank weight loss, otitis media, and at times aspiration pneumonia, atelectasis or even asphyxia.

It is the purpose of this paper to present in condensed form the major causes of vomiting in infancy and childhood. Etiology will be stressed and treatment will be referred to only briefly.

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Vomiting in the Newborn Period

Gastric irritation—Meconium or blood swallowed during labor and delivery may cause sufficient gastric irritation to produce vomiting in the first day or two after delivery. Simple gastric lavage ordinarily suffices to correct this condition.

Babies born by cesarean section and those born of diabetic mothers tend to have more amniotic fluid in the stomach than other infants. Gastric lavage is advised for these infants in order to prevent regurgitation of amniotic fluid that may result in aspiration into the lungs.

Hematemesis—A special problem arises

when a newborn baby vomits blood. One should determine immediately by the alkaline denaturation test of Apt whether the blood contains predominantly adult hemoglobin (representing blood swallowed by the baby in the process of delivery or sucked later from a fissured nipple) or fetal hemoglobin (blood loss from the baby himself). The test is performed by adding 5 to 10 parts of tap water to one part of grossly bloody vomitus, centrifuging the resultant hemoglobin solution, decanting or filtering the supernatant fluid, and mixing 1 ml. of 1 per cent solution of sodium hydroxide with 5 ml. of the hemoglobin solution. If two minutes later the solution remains pink, it indicates that fetal hemoglobin is present (blood derived from the baby, perhaps indicating a serious condition). If the solution turns brownish-yellow, the test indicates the presence of adult hemoglobin (blood derived from the mother, an innocuous event).

If the blood has come from the mother, gastric lavage suffices to correct vomiting. If the mother has a fissured nipple, nursing from the affected breast is prohibited.

When the alkaline denaturation test indicates that the baby is vomiting his own blood, one should make appropriate examination and tests for sepsis, blood dyscrasias, hypoprothrombinemia and, rarely, peptic ulcer. A blood culture should be obtained and one should determine bleeding time, clotting time and prothrombin time and evaluate clot retraction. Gastrointestinal x-ray studies may be required.

Treatment is, of course, directed toward correction of the causative condition and also includes blood transfusion.

Intracranial conditions—Vomiting in the newborn period may also be due to increased intracranial pressure, as from hemorrhage, edema, hydrocephalus or, rarely, meningitis. Subdural hematoma usually has not achieved sufficient size to cause vomiting in the first week or two, but it may be a cause later. When a newborn infant vomits, one should always think of these possibilities and then evaluate accordingly.

Acute infections—Overt and occult infections in the newborn period may produce vomiting. Unfortunately the newborn infant often fails to exhibit fever with infection. Furthermore the leukocyte count is frequently valueless because it is ordinarily high in the first days of life. However, one may note an infected umbilicus, impetigo, diarrhea or symptoms referable to the respiratory tract. Examination of the urine may show pyuria. A chest roentgenogram may reveal unsuspected pneumonia. A blood culture may identify the causative organism. Treatment depends on the causative condition.

Feeding methods and composition of food—Improper feeding methods or composition of food frequently accounts for vomiting in the newborn period and the first months of life. The most common offender here is overdistention of the stomach with milk and air through failure to feed babies in the upright position and to "bubble" them during and after the feeding. Certain infants vomit when fed concentrated formulas, those prepared from unboiled sweet milk, acid milk formulas, greatly diluted formulas which lead to excessive intake and overdistention, those too rich in fat, and those prepared from milk that has been frozen. Furthermore, some infants are allergic to cow's milk and vomit when it is ingested. Infants recovering from an acute illness such as gastroenteritis may have such a temporary depression of hydrochloric acid and digestive enzymes that they vomit feedings that are not sufficiently diluted and low in fat content.

The recent trend to serve neonatal banquets in order to show just how tolerant a newborn baby's stomach can be is also a cause of vomiting. It would be sensible if we would only remember that we are trying to feed babies what they can digest easily rather than trying to test them with the latest fashions in early introduction of foods.

Congenital anomalies of the alimentary tract—The alimentary tract is a favorite site for anomalies, and obstructive vomiting associated with constipation and perhaps abdominal distention should always suggest such a possibility.

Atresia of the esophagus—This condition is easy to diagnose because the baby has ex-

FIGURE 1. Esophageal atresia showing outline of upper blind pouch. Presence of air in intestinal tract proves concomitant presence of tracheo-esophageal fistula.

cessive secretions welling from the mouth, often requires pharyngeal suction, chokes and sputters and perhaps becomes cyanosed when fed, and one cannot pass a catheter to the stomach. The site of the obstruction can be outlined by esophageal roentgenography with a small amount of opaque medium (figure 1). Treatment is surgical. Antibiotics are given to control the often-associated aspiration pneumonia, or atelectasis.

Chalasia and achalasia—Chalasia or failure of the pinchcock mechanism of the lower end of the esophagus to close properly permits regurgitation of milk, especially when the infant is in a horizontal position. Diagnosis is established by roentgenography. Treatment consists of feeding the infant in an upright position, thickened feedings, and maintaining him upright after feedings by propping or use of a specially constructed tiny chair.

Achalasia or cardio-esophageal spasm is rarer, results in inability to pass food from the esophagus to the stomach, and causes regurgitation, sometimes with aspiration of food into the lungs. Roentgenograms aid in diagnosis.

Congenital diverticulum of the esophagus is even rarer and may result in regurgitation of unchanged food.

Diaphragmatic hernia—Herniation of the stomach, intestines or other organs into the thoracic cavity may exist without producing symptoms in the newborn period, but more often vomiting does occur in the neonatal period. Obstructive vomiting associated with dyspnea and perhaps cyanosis should always suggest this entity. Roentgenograms prove the diagnosis. Treatment is surgical.

Pyloric stenosis—This famous cause of vomiting in the newborn period is quite easy to diagnose. Typically, vomiting starts in the second or third week and becomes more frequent and forceful, appetite is avid, stools are reduced in number and volume, weight gain fails, weight loss ensues, dehydration follows, urine becomes scanty, and visible peristaltic waves become apparent. Shallow, irregular respirations may occur, indicating severe alkalosis. Alkalotic tetany rarely ensues. One may be able to palpate a pyloric tumor. Roentgenograms in the right anterior oblique position show delay in gastric emptying, a narrow, elongated pyloric canal ("string sign"), and crescentic duodenal deformities (figure 2). Complications may include malnutrition, hypoproteinemia, anemia, intercurrent infection and hypokalemia.

In the United States, favored treatment of pyloric stenosis includes proper preoperative preparation, performance of the Fredet-Ramstedt operation, and careful postoperative feeding. Preoperatively it may be necessary to correct dehydration, alkalosis, hypokalemia and anemia and to treat infection. Abroad, medical management has authoritative adherents.

Duodenal obstruction—There are four main causes of duodenal obstruction: (1) atresia or complete obstruction by an intraluminal diaphragm, (2) congenital stenosis, (3) compression associated with malrotation of the colon, and (4) encirclement by an annular pancreas. In all instances treatment is surgical.

In atresia, vomiting occurs on the first day of life, the vomitus contains bile, there is often upper abdominal distention, and the plain

roentgenogram shows the "double bubble" sign (marked distention of the stomach and a lesser distention visible in the duodenum, with the remainder of the bowel devoid of air). In such a case the use of opaque media in roentgenography is superfluous and time-consuming, may impose technical difficulties at operation, and may result in aspiration of the vomited material.

Duodenal stenosis is a less severe lesion and it is usually readily diagnosed by the use of roentgenography.

In malrotation of the colon, tissue bands often cross and compress the duodenum, leading to obstructive vomiting in the newborn period or later. Barium enema roentgenography reveals the presence of malrotation, and studies of the duodenum with opaque media show the compression.

A diagnosis of annular pancreas can usually be established preoperatively by contrast roentgenography (figure 3). Although the entity may exist without obstructive vomiting, we have seen several infants with this condition who have started vomiting within the first weeks of life. Treatment consists of a bypassing operation. Division of the encircling pancreatic tissue is dangerous from the standpoint of producing a fistula.

Other atresias or stenoses—These may occur in the jejunum or ileum and less often in the colon. Rectal atresia is obviously easy to diagnose because of the usual absence of the

FIGURE 2. Pyloric stenosis. Right anterior oblique view showing elongation and narrowing of the pyloric canal with crescentic deformity of the base of the duodenal cap.

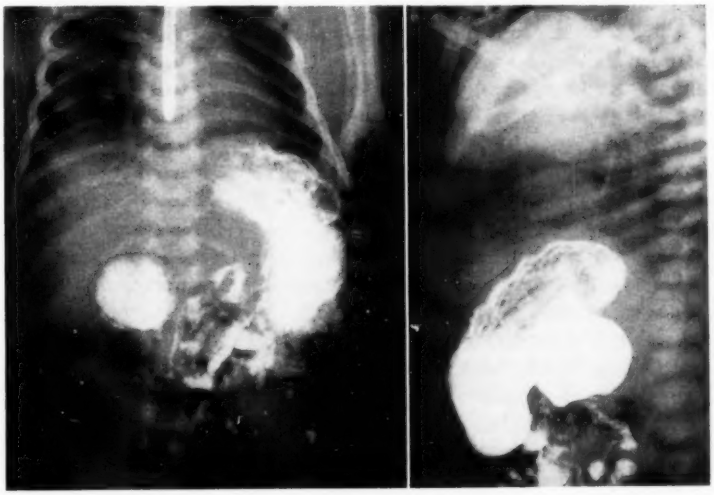

FIGURE 3. Annular pancreas. Left film shows end-on view of large dilated proximal duodenum. Right film shows dilated duodenum with abrupt termination at point of annular constriction.

FIGURE 4. Plain roentgenogram of patient with meconium ileus, showing calcific deposits in the peritoneum.

anus. In stenosis, digital discovery of rectal constriction proves the point.

Volvulus—A most dangerous form of intestinal obstruction in the newborn period, or afterward, is volvulus, a condition in which the small bowel twists upon itself. This is usually due to an abnormally small posterior attachment of the mesentery, which arises as a slender stalk and spreads out like a Japanese fan. Volvulus is usually associated with malrotation of the colon. Besides obstructive vomiting, fever and shock develop and there is a marked tendency to bacteremia and melena. Early operation is mandatory. Academic diagnostic delay may prove fatal.

Aganglionic megacolon (Hirschsprung's disease)—Obstructive vomiting may occur in the newborn period because of this condition in which the intramural myenteric plexuses are lacking in the rectum, sigmoid and perhaps other areas of the colon. Diagnosis is somewhat difficult, but failure to expel a barium enema suggests the condition and anal biopsy to reveal lack of myenteric plexuses may prove the diagnosis. Treatment in the newborn period is difficult and temporizing. A transverse colostomy is usually required to permit survival until the definitive pull-through operation of Swenson can be performed.

Meconium ileus—About 10 per cent of infants with cystic fibrosis of the pancreas have obstructive vomiting in the newborn period because of meconium ileus. Lack of pancreatic enzymes results in viscid, mucilaginous meconium that is difficult to propel by peristaltic activity. Diagnosis may be suggested by a history of siblings who have had cystic fibrosis of the pancreas, palpation of doughy masses in the region of the terminal ileum, and by a plain roentgenogram of the abdomen that may reveal a stippled appearance in the region of the terminal ileum, with or without calcific plaques in the peritoneum (figure 4). Operation is indicated in practically all cases and is difficult. A double-barreled ileostomy is often the procedure of choice.

Adrenocortical insufficiency—Although not an alimentary tract anomaly, this condition can so simulate obstructive vomiting that it is considered here. Several patients with this entity have been operated on under the erroneous diagnosis of pyloric stenosis. At times the infant looks like one with hypospadias and undescended testes, the elongated clitoris resembling a penis. In the male infant the penis may be larger than normal and the scrotum more heavily pigmented than normal.

There is excessive androgenic output from the adrenal cortex, and production of electrolyte-controlling and carbohydrate-controlling hormones is diminished.

The typical clinical picture in the newborn period consists of failure to regain birth weight, polyuria, severe and recurrent dehydration, vomiting, acidosis, low serum sodium and chloride, azotemia and a tendency to hyperkalemia. The urinary excretion of 17-ketosteroids is increased. Treatment consists of parenteral fluid therapy, injections of desoxycorticosterone acetate (DOCA®) (usually about 2 to 3 mg. per day), daily addition of about 2 to 3 gm. of sodium chloride to the formula, administration of cortisone to depress excessive androgenic production, and

subsequent long-term management with desoxycorticosterone acetate, salt and cortisone.

Vomiting After the Neonatal Period

After one month of age the causes of vomiting become more varied and often more difficult to diagnose. Some of the conditions previously mentioned may persist past one month to cause continuation of vomiting. Feeding methods and food composition often cause emesis in the early months. Acute infections become more frequent and emesis is often an early symptom. Psychogenic vomiting increases in frequency during the first years.

Rumination—Infants with this condition regurgitate small quantities of sour, curdled milk from time to time throughout the day, either spontaneously or when picked up or leaning forward. Esophagrams are usually normal. Bubbling the baby during and after feedings, placing him on his right side after feedings to facilitate emptying of the stomach, and use of thickened feedings may help solve this annoying problem.

Enteric infections—Gastroenteritis often produces vomiting as well as diarrhea. Treatment involves proper fluid and electrolyte therapy, a period of initial starvation of 12 to 24 hours, and then careful feedings of small amounts of a well-diluted skim milk formula in increasing quantities. Antibiotic treatment may help. Vomiting may be prevented or diminished in frequency by barbiturates given intramuscularly or rectally, or by chlorpromazine injected intramuscularly.

Parenteral infections—The most common cause of vomiting in infants past one month of age who have been well adjusted to feedings is the onset of an acute infection, usually in the upper part of the respiratory tract. Vomiting may precede overt evidence of infection such as fever or pharyngeal hyperemia.

Such vomiting is often controlled by permitting frequent small sips of a simple carbohydrate-containing fluid such as COCA-COLA®, by use of barbiturate suppositories, or by use of chlorpromazine (THORAZINE®). When dehydration and acidosis ensue, vomiting is difficult to control unless fluid and electrolyte balance is restored.

Abdominal conditions—A variety of abdominal conditions other than simple enteric infections may produce vomiting. These include appendicitis, peritonitis, diverticulitis, mesenteric adenitis, intussusception, other forms of intestinal obstruction, hepatitis and peptic ulcer. Treatment of each of these conditions is too well known to describe here.

Intestinal obstruction—Intestinal obstruction after the newborn period may be due to peritonitis, adhesions or lesions that produce partial obstruction and did not manifest themselves in the first month of life. Among the latter are some cases of diaphragmatic hernia, intestinal stenoses, malrotation of the colon, and duplication of areas of the bowel. Gastrointestinal x-ray studies are often diagnostic. Treatment is surgical.

Urinary tract—Acute pyelonephritis associated with fever may initiate emesis. Congenital obstructive uropathies associated with infection also produce vomiting, often associated with abdominal pain. Patients with unexplained recurrent abdominal pain, with or without vomiting, always deserve repeated careful examination of the urine and excretory urograms.

Intracranial conditions—Intracranial infections, neoplasms, hemorrhage and subdural hematoma may all produce vomiting and should be thought of when other causes of emesis are not found. Poisons or toxins acting on the brain may also produce vomiting. A good example is lead encephalopathy.

Bacterial meningitis produces vomiting in many cases, as does encephalitis.

Subdural effusion as a complication of bacterial meningitis deserves emphasis. This, too, is a lesion that may cause vomiting. Subdural taps may prove effective treatment.

Head trauma may cause vomiting because of the fright of the experience or because of concussion with edema or hemorrhage.

Endocrine conditions—Adrenocortical insufficiency in the newborn infant has been mentioned as a cause of vomiting. Vomiting may also occur in the crises of hyperthyroidism, diabetic acidosis and hypoglycemia. Treatment is related to management of the underlying condition.

Epidemic vomiting—At times there are community epidemics of an acute infectious disease characterized by severe vomiting, fever, pharyngeal hyperemia and perhaps diarrhea and abdominal pain. Treatment involves strict bed rest, frequent small sips of a carbohydrate-containing liquid such as a soft drink given in increasing amounts, use of chlorpromazine or barbiturate suppositories, and then discreet feeding of broth, clear soups, soda crackers, JELL-O®, and other easily assimilated foods.

Cyclic vomiting—Certain children have recurrent bouts of vomiting for which no cause can be found, or at the onset of trivial infections. Treatment is the same as described for epidemic vomiting, with perhaps more necessity in the usual case for parenteral fluid therapy.

Psychogenic vomiting—Emesis on an emotional basis is far more common than generally supposed. It stems from a wide variety of tension-producing situations in the home, school, neighborhood or elsewhere. Abdominal pain often occurs prior to such vomiting. In every case of unexplained recurrent vomiting the physician should consider carefully the psychologic factors.

Allergic vomiting—Children sensitive to various foods may react by vomiting when they ingest these foods. At times they also have severe abdominal colic and diarrhea. There may be blood in the stools, and mucus, perhaps rich in eosinophils. A food diary assists in detection of these cases, as does a strong history of allergy in the patient and his family. Skin tests are of less value but elimination diets may aid in detection of the offending food. Withdrawal of the offending foods from the diet is the obvious treatment.

Dietary indiscretions—Dietary indiscretion as a cause of vomiting is far less common than generally supposed. There is too much of a tendency, especially among parents, to ascribe emesis to what the child has eaten. The circumstances in which the dietary indiscretions occur may be more important than the food itself. Thus, on long automobile drives across country the combination of car motion, hurried eating, heat and fatigue may result in vomiting food that is ordinarily tolerated.

Reflex vomiting—Vomiting may occur in any disease characterized by severe bouts of coughing or by accumulation in the stomach of abundant mucopurulent exudate from a heavy postnasal drip, or may result from the pressure of a tongue depressor.

Motion sickness—Vomiting from riding in an automobile, train, airplane or boat can be minimized if DRAMAMINE® or BONAMINE® is given to the child before the trip begins.

Drugs and anesthesia—The induction of anesthesia is often associated with vomiting, which is particularly dangerous if the stomach contents were not removed by suction prior to operation. Various drugs may also produce vomiting, including digitalis, sulfonamides, broad-spectrum antibiotics and even acetylsalicylic acid.

Familial autonomic dysfunction (Riley-Day syndrome)—In this peculiar, recently described syndrome occurring in Jewish children, there may occur cyclic bouts of vomiting lasting two or three days and recurring at intervals of weeks or months. Other findings in this entity include failure to produce tears, excessive perspiration, blotchy skin eruptions, drooling, indifference to pain, hypoactive deep tendon reflexes, awkwardness, labile blood pressure, and sometimes mental deficiency, pulmonary infections and corneal ulcerations.

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The Accidental Chemical Poisoning Problem

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In the United States, accidents are the leading cause of death and disability of persons from 1 to 34 years of age inclusive. Accidents were responsible for 94,000 deaths and 9,000,000 injuries in this country in 1955. Home accidents were responsible for 28,000 deaths, and 20 per cent of these deaths occurred in children who were less than five years of age.[1] The number of children in this age group who died of accidents in New York City in 1955 was more than three times as great as the number who died of the 10 leading communicable diseases combined (figure 1).

It is estimated that more than 400 children who are less than five years of age die each year of chemical poisoning in the United States. This is four times the number of children of this age who die each year of chemical poisoning in England.[2,3] Twenty-seven (14.4 per cent) of children less than five years old who died of accidents in New York City in 1955 died as a result of poisoning. Owing to the rapid progress that is being made in science and technology, and owing to the increasing number of new drugs and household preparations that are being introduced, the risk of accidental chemical poisoning is increasing.

Owing to the increase in the child population, an increasing number of susceptible persons are being exposed to these potential hazards. As a result, there has been an alarming and continual increase in the incidence of accidental poisoning. It is evident that this is a major problem of public health significance, and that an all-out interdisciplinary effort must be directed toward its solution.

The reporting of cases of poisoning by drugs and by the inhalation or ingestion of other toxic agents has been mandatory in New York City for many years,[4] but only a small percentage of the cases has been re-

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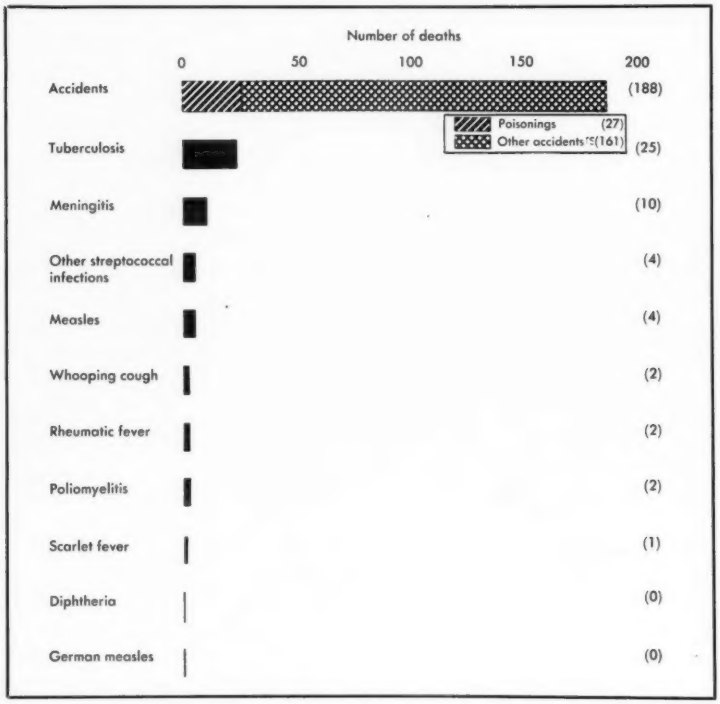

FIGURE 1. Certain causes of death of children under five years of age in New York City, 1955.

ported. Prior to the establishment of the Poison Control Center, the number of cases that were being reported annually did not exceed several hundred.[5] Since the establishment of this center in March 1955, more than 8000 cases have been reported by physicians and hospitals. Even this alarming number does not tell the entire story, and it is still grossly understated since in many cases of accidental poisoning the condition is not recognized or is diagnosed erroneously. If the symptoms are not severe and are amenable to first-aid measures in the home, the episode usually is not reported by the physician or the family. The reports in the main do not include such therapeutic hazards as overdosage, reactions and complications. Apparently, such incidents are not yet included in the traditional medical thinking of poisoning, and hence are not reported. It is believed, however, that New York City is fortunate in having a law which makes it mandatory that all such cases of poisoning be reported.

Epidemiologic Consideration

If any substantial inroad is to be made in the chemical poisoning problem, it will be necessary to obtain a great deal more information than is now available. A sound and effective control program is not possible without reliable information about the causes and the various determining and contributing factors.

Gordon[6] and Roberts and Gordon[7] were among the first to emphasize the importance of an epidemiologic approach in accident control. They aptly stated that accidents follow the same basic epidemiologic patterns as do disease processes. Intensive epidemiologic investigations have been conducted by the New York City Department of Health for the past few years. They have been designed to obtain more precise information about the natural history of accidental poisoning; that is, how, why, where and when the poisoning occurred, and the person who was poisoned.

FIGURE 2. Substances responsible for chemical poisoning in 4,469 cases.

It is believed that the toxic agent, the host, the environment and their relationship must be fully investigated before sound countermeasures can be formulated. These investigations are being carried out in the following manner.

Physicians and hospitals immediately report all cases of accidental chemical poisoning on a prescribed form. After the patient has been dismissed, the hospital promptly reports on a designated form the signs and symptoms, the type of therapy, the outcome, and other relevant data.

In order to obtain additional data, an experienced public health nurse visits the home of all poisoned children who are less than 16 years of age. To complete the epidemiologic investigation, data are obtained on the biologic, physical, cultural and social environment of the family. Information also is obtained on the age, sex and color of the patient, the toxic agent, the time of day at which the poisoning occurred, the mode of its occurrence, the activity of the child when the poisoning occurred, the type of supervision, the locale, the type of treatment, the preventability, and the outcome. Inquiry also is made as to whether the child has had a previous accident. The nurse also is requested to report whether any other health problems exist in the home. If they do, action is taken to eliminate them, and a follow-up study is made. The nurse returns the report to the Poison Control Center for analysis and necessary action. The completed form is then forwarded to the Bureau of Statistics for tabulation and analysis.

Material

During 1956, 5,014 cases of poisoning were reported to the Poison Control Center. The number of individual products responsible for the poisoning in these cases comprised several hundred (figure 2). Some products

TABLE 1

AGENTS RESPONSIBLE FOR POISONING IN 5,014 CASES*

AGENTS	CASES
Internal medicines	2,794
External medicines	456
Rodenticides	119
Insecticides	171
Disinfectants	183
Detergents	392
Polishes	73
Solvents	198
Cosmetics	137
Miscellaneous agents	491
Total	5,014

*Cases reported to the Poison Control Center of the New York City Department of Health during 1956.

TABLE 2

TYPE OF POISONING ACCORDING TO AGE OF PATIENTS*

TOXIC AGENTS	CASES	AGE OF PATIENTS (*Years*)						
		Under 2	2	3	4 to 9	10 to 19	19 or more	Unknown
Internal medicines	2,421	131	319	178	101	166	1,456	70
Aspirin	567	51	175	105	43	66	122	5
Barbiturates	950	9	16	5	6	34	849	31
Other internal medicines	904	71	128	68	52	66	485	34
External medicines	419	73	47	14	27	38	206	14
Cosmetics	112	37	38	11	7	7	7	5
Household preparations and solvents	810	264	189	63	61	32	180	21
Bleaching agents	182	44	44	15	15	7	52	5
Lye	74	15	15	10	8	4	22	—
Other preparations	554	205	130	38	38	21	106	16
Insecticides	161	43	38	11	9	6	44	10
Rodenticides	106	37	16	13	10	4	25	1
Miscellaneous agents	440	150	95	38	51	16	69	21
Lead	111	36	40	13	13	1	7	1
Other agents	329	114	55	25	38	15	62	20
	4,469	735 (16%)	742 (17%)	328 (7%)	266 (6%)	269 (6%)	1,987 (45%)	142 (3%)

*As reported to the Poison Control Center of the New York City Department of Health in the first 11 months of 1956.

included as many as 12 different brands. For convenience, the substances have been classified in major categories as are shown in table 1. Four thousand four hundred and sixty-nine of the 5,014 cases were reported in the first 11 months of 1956. The present paper will be based mainly on a review of this group of 4,469 cases.

Etiology

Age—The age of the patients was known in 4,327 of the 4,469 cases. In 2,340 (54 per

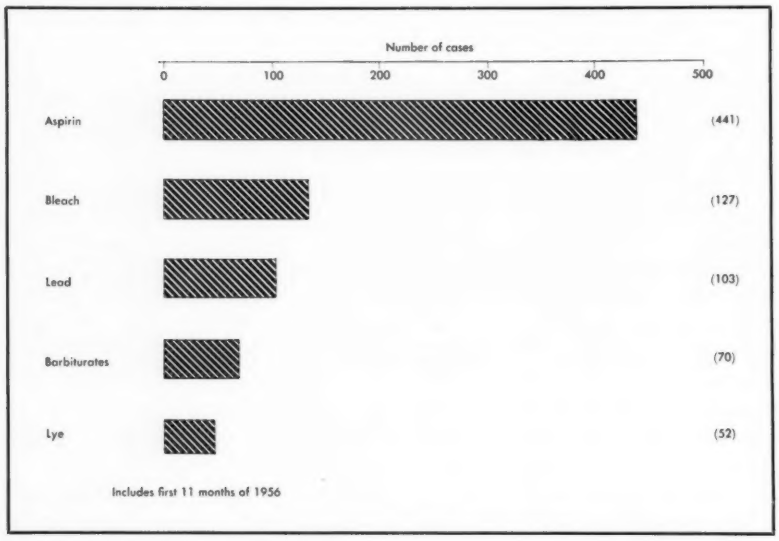

FIGURE 3. Five leading causes of poisoning in children less than 19 years old.

cent) of the 4,329 cases, the patients were known to be less than 19 years of age. Of the patients in these 2,340 cases, 735 (31 per cent) were less than two years old, 742 (32 per cent) were two years old, and 328 (14 per cent) were three years old (table 2). Therefore, 1,805 (77 per cent) of the 2,340 patients were less than four years old.

The high incidence of poisoning in children who are two years or less of age may be attributed to the particular stage of growth and development of children of this age. These children are avid explorers and "mouthers." Their poisoning frequently is the result of exposure of toxic agents in an unsafe place in the home of an inexperienced person. As children become older, they become more cautious, and there is a striking decrease in the incidence of poisoning. Two year old children who are particularly mobile and are able to climb to high places, such as medicine cabinets, bureaus, television sets and other storage places, frequently are victims of poisoning by drugs intended for internal administration. As a result, there is a close relationship between the accessibility of toxic agents and the occurrence of poisoning.

Sex and race—Previous reports[8,9] have indicated that the incidence of poisoning is higher among boys than it is among girls, and that it is higher among nonwhite children than it is among white children. The results of the epidemiologic study reported in the present paper confirm these findings. The higher incidence among nonwhite children most likely is attributable to social and economic conditions such as poor housing and overcrowding rather than to any constitutional difference.

Toxic agents—Although more than 200 different substances were responsible for the poisoning in the entire group of 4,469 cases, five substances accounted for the poisoning in 34 per cent of the 2,340 cases in which the patients were known to be less than 19 years old (figure 3).

Drugs intended for internal administration were responsible for the poisoning in 2,421 (54 per cent) of the entire group of 4,469 cases (table 2 and figure 4) and in

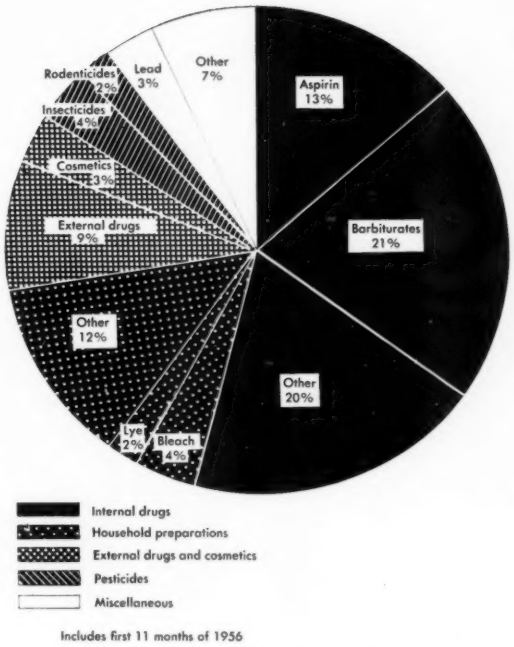

FIGURE 4. Substances responsible for poisoning in 4,469 cases.

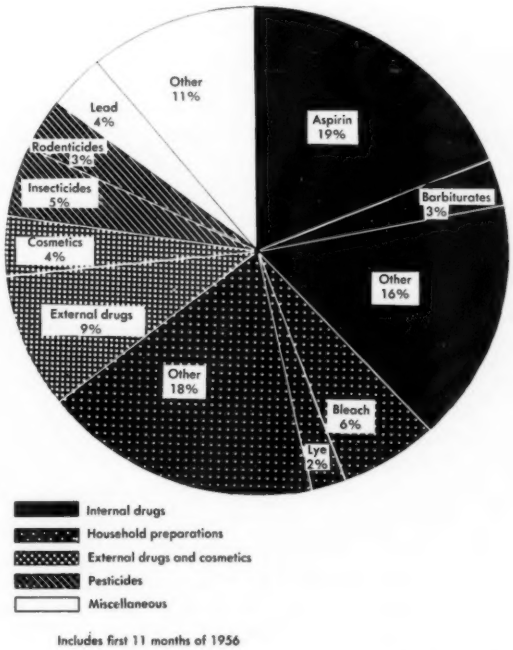

FIGURE 5. Substances responsible for poisoning in 2,340 cases in which the patients were known to be less than 19 years of age.

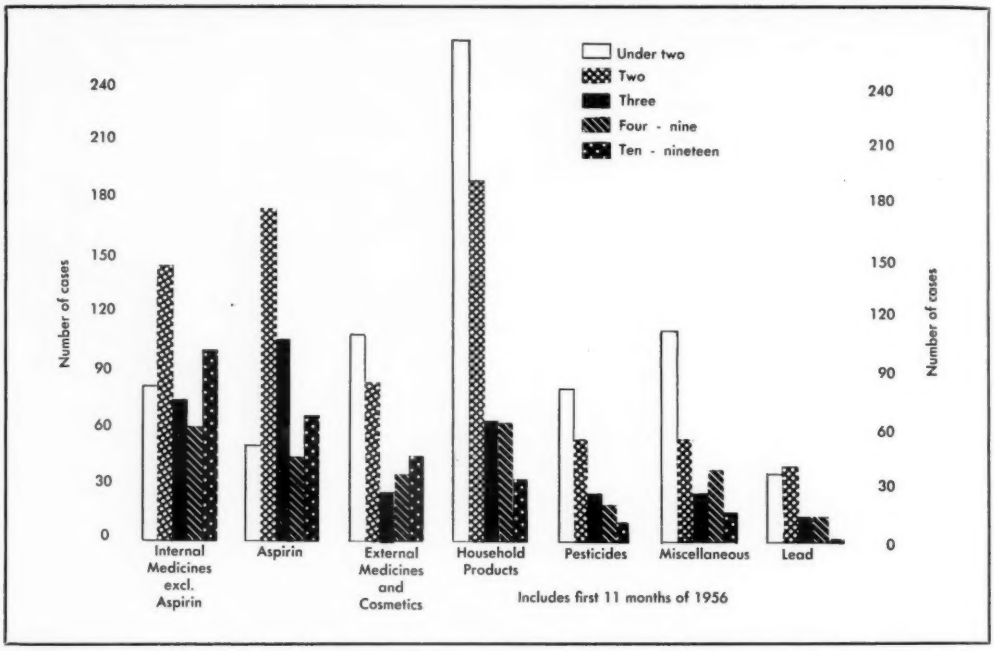

FIGURE 6. Relation of toxic agent to age of patients in 2,340 cases of poisoning in which the patients were known to be less than 19 years of age.

895 (38 per cent) of the 2,340 cases in which the patients were known to be less than 19 years old (figure 5). Figure 6 shows the relationship between the agent responsible for the poisoning and the ages of the patients in this group of 2,340 cases. Aspirin was responsible in 567 of the entire group of 4,469 cases. Flavored baby aspirin was a very common cause of poisoning. This undoubtedly reflects the common use of this preparation in the home. A fatal poisoning occurred in one case in which 5 gr. of aspirin was administered to a six week old infant every four hours for seven days.

Barbiturates were the cause of the poisoning of 70 children who were less than 19 years old, and two of the children died. In each instance, the aspirin was self-ingested. The unwarranted claims of manufacturers of nonbarbiturate sedatives and tranquilizing agents and the indiscriminate use of such drugs constitute a grave potential hazard, since the drugs frequently are readily accessible to children in the home. During 1956, about 100 cases of poisoning by tranquilizing drugs were reported to the Poison Control Center, whereas only 12 such cases were reported in 1955.

In one case, the poisoning was due to PRELUDIN®, a new anorexic drug. It is possible that this may be the first reported case of poisoning by this drug. The symptoms in this case (case 21) were alarming and were very similar to those of amphetamine intoxication, although the structure of Preludin differs from that of the amphetamine drugs.

Household preparations were the cause of the poisoning in 609 (26 per cent) of the 2,340 cases in which the patients were known to be less than 19 years old (figure 5). Bleaching agents were the most frequent offenders in this category. Children who were two years old were the most frequent victims of poisoning by household preparations. Those who

TABLE 3

RELATION OF LEAD POISONING TO RACE, SEX AND AGE*

RACE AND SEX	CASES	AGE (Years)					
		Under 2	2	3	4	6	7 to 19
White							
Male	7	5	2				
Female	14	4	7‡	2		1	
Negro							
Male	22	11	5	5			1
Female	15	10†	2	3			
Puerto Rican							
Male	16	8‡	6	1	1		
Female	20	6	6‡	5‡	3		
	94	44	28	16	4	1	1

*In cases in which the patients were less than 19 years old.

†Death occurred in one case.

‡Death occurred in two cases.

were between two and three years old were most frequently victims of medicines, such as aspirin, which were intended for internal administration. This again illustrates the relationship between poisoning and the child's stage of growth and development. The infant who is still crawling on the floor and cannot reach high places is more likely to be poisoned by a substance which is available at a low level, and hence is particularly susceptible to poisoning by household preparations which generally are stored on the floor or under the kitchen sink.

Bleaching agents were the cause of the poisoning in 125 (6 per cent) of the 2,340 cases in which the patients were known to be less than 19 years old (figure 5). Creepers and toddlers were the chief victims of poisoning by these agents. Lye was responsible for the poisoning in 52 cases in which the patients were known to be less than 19 years of age (table 2). Children who were less than four years old were most susceptible to poisoning by this agent. In 40 (77 per cent) of the 52 cases, the children were less than four years old. Death occurred in one case in which the patient was a three year old boy. Fatal poisoning also has been caused by the ingestion of furniture polish.

Naphthalene poisoning is encountered regularly, particularly during the summer months. It is urged that the use of such terms as camphor balls and moth balls be discouraged, since such preparations actually contain either naphthalene or paradichlorobenzene. The identification of the ingredients of such preparations by the odor is not reliable because the odor of naphthalene is likely to be confused with that of paradichlorobenzene. The only safe procedure is to examine the original container, if it is available, or to obtain the information from the seller. Naphthalene is absorbed rapidly in spite of the fact that it is commonly considered to be insoluble. It is worth emphasizing that the ingestion of only one moth ball may prove fatal for a child.

In 419 (9 per cent) of the 4,469 cases, the poisoning was due to drugs that were intended for external use (figure 4). In 1,094 (47 per cent) of the 2,340 cases in which the patients were known to be less than 19 years old, the poisoning was caused by medicines that were intended for internal or external use (figure 5).

Oil of wintergreen is a frequent cause of poisoning, and it caused death in three cases in this series. In two of the cases, the children were 13 years old; in the remaining case, the child was two and a half years old. One of the 13 year old children mistook the

oil of wintergreen for water, and the two and a half year old child picked up a bottle of oil of wintergreen from the dresser and ingested its contents. Although the child was taken to the hospital immediately, she died on the following day.

Cosmetics were responsible for the poisoning in 112 cases.

One hundred and eleven cases of lead poisoning were reported. When a case of this type is reported, an investigation is conducted by the Bureau of Preventable Diseases. This investigation includes chemical analysis of a specimen from the source of the poison, determination of the concentration of lead in the blood, other laboratory tests, and a clinical examination. In 94 of the 111 cases, the diagnosis of lead poisoning was confirmed by the Bureau of Preventable Diseases. In 103 of the 111 cases, the patients were less than 19 years old. Only 21 (22 per cent) of the 94 children were white (table 3); the remaining 73 (88 per cent) were Negroes or Puerto Ricans. This is in marked contrast to the general population of New York City, which is 75 per cent white. This disparity probably is a reflection of environmental factors, particularly substandard houses which contain several coats of lead paint. In such houses, flakes of plaster and paint peelings from window sills are easily accessible to young children. Incidentally, in all of the 94 cases, the history revealed that the affected children had chewed flakes of plaster or paint peelings. In such cases, the poisoning is due to inadequate adult supervision or to a lack of awareness of adult members of the family about the harmful effects of lead. In every case, a parent would tell the public health nurse, "I didn't know that chewing plaster was harmful."

No significant difference was noted in the incidence of the disease according to sex, although it occurred far more frequently in white girls than it did in white boys (table 3). It is significant that seven of the nine deaths occurred in girls, but the number of cases in this group is too small to warrant any valid conclusion as to whether girls are more vulnerable to this type of poisoning than are boys.

In 72 (77 per cent) of the 94 cases of lead poisoning in which the patients were less than 19 years old, the poisoning occurred in children who were in the first three years of life (table 3). Death occurred in nine of the 94 cases, and seven (78 per cent) of the nine deaths occurred in children who were in the first three years of life.

Thirty-eight per cent of the 94 cases of lead poisoning were reported from two districts in Brooklyn. (New York City is divided into 30 health districts.) Four of the deaths which resulted from lead poisoning occurred in these two districts. Sixty per cent of the cases were reported from one of the five boroughs, and 67 per cent of the deaths occurred in this borough. The social and economic status was low in the districts in which the incidence of the poisoning was highest. The hospitals in these districts are keenly aware of the lead poisoning problem. Their staff physicians have developed great skill in the diagnosis of this type of poisoning, and they are carrying on an intensive search for cases of this disease.

The seasonal incidence of lead poisoning is interesting. Fifty-one per cent of the cases were reported between June and September.

Time and place of occurrence—Accidental poisoning usually occurs between noon and 6 P.M. The next most dangerous period is between 6 A.M. and noon. This is understandable since children usually are up and engaged in play during these hours. The kitchen was found to be the most dangerous place in the house so far as poisoning is concerned, and the bedroom was the next most dangerous place.

Season—Except in cases of lead poisoning, the seasonal incidence was not significant, although naphthalene poisoning was most common during the spring and summer months and mistletoe poisoning was most common during the Christmas season.

Supervision—In most cases in which the patients are children, poisoning happens with lightning rapidity and when adult supervision is lacking.

Persons who administered the toxic agent—In about 90 per cent of the cases, the poison was self-administered. In a very small

number of cases, the poisoning was due to overdosage or to mistaken identity and administration by an adult. In about 100 cases in which the children were between 10 and 19 years of age, it was suspected that the children had tried to commit suicide or had taken the toxic substance to attract attention. Epidemiologic investigation confirmed this suspicion in 47 cases.

Relation of poisoning to removal of toxic substance from the original container—The storing of potentially hazardous substances in household utensils was a contributory cause of the poisoning in many cases. Oil of wintergreen, carbon tetrachloride, kerosene, benzene, turpentine, ammonia, furniture polish, and insecticides and rodenticides were stored in saucers, drinking glasses, soda bottles, mayonnaise jars, coffee cans, milk bottles and fruit jars. In more than 50 per cent of the cases in which the poisoning was due to bleaching agents, solvents, ammonia, and insecticides and rodenticides, these substances were not in their original containers when the poisoning occurred.

This practice is particularly common among certain ethnic groups who purchase household preparations in gallon jugs in order to save money. They then divide the preparation with other families in the same ethnic group, and the preparations usually are stored in such containers as glasses and soda bottles. This highlights the relationship between poisoning and culture, custom and tradition.

In addition to not being in their original containers, most of the toxic agents were in open places such as on tables, shelves, floors, in open drawers, under sinks or on window sills. In only 6 per cent of the cases were the toxic agents stored in medicine cabinets, and the cabinets usually were unlocked. In many cases, the toxic agent was in a handbag which was given to the child to play with. The poisoning frequently occurred in the home of a grandparent.

Other contributing factors—The evil practice of hospital pharmacies of dispensing drugs in small collapsible cardboard containers also is responsible for many instances of poisoning. In addition, these containers do not show the name of the hospital, the name of the drug or any caution regarding its administration. They merely contain instructions for the patient to take one tablet or one teaspoonful every three or four hours. This insidious practice makes identification of the toxic agent difficult and thus delays prompt and appropriate treatment.

The placing of containers of similar size, shape and color, and with similar labels, in medicine cabinets not infrequently will lead to mistaken identity and errors in medication. In one hospital, tincture of benzoin was administered instead of paregoric and one sedative was given instead of another. It is surprising that more instances of poisoning do not occur in hospitals, since many medicines usually are stored on bedside tables and cabinets in pediatric wards and in dressing rooms where they are within easy reach of children.

Accident proneness—A history of a previous accident was obtained in only 12 per cent of the 2,340 cases. A family history of an accident was obtained in 13 per cent of the cases reviewed.

Other hazards and public health problems—Other hazards found in the home by the public health nurses included defective plumbing, defective gas appliances, gas odors, peeling of plaster and paint, vermin, broken windows and unguarded windows. Such hazards were found in more than 25 per cent of the homes visited. It is not known whether this incidence of such hazards is higher than it is among the general population.

In addition to these hazards, this epidemiologic investigation disclosed other public health problems, such as pregnancy without prenatal care, lack of health supervision of infants and children, emotional and mental problems, tuberculosis and other chronic diseases without needed medical care, and a host of other conditions which at times were far more important than the original accident for which the visit of the public health nurse was made. Happily, the public health nurses were able to help the families with these problems, and appropriate action was instituted in more than 90 per cent of the cases in which such problems existed.

Mode of Occurrence of Poisoning

In order to emphasize the relation between the accessibility of toxic agents and the occurrence of poisoning, I shall briefly summarize several cases which were reported to the Poison Control Center.

Case 1—While a white girl, aged two years, was playing in a vacant lot, she found a can of lye. She brought it home and ate an unknown quantity of it. She complained of burning of the mouth, and she was taken to the hospital. Examination disclosed lye burns of the pharynx. Cortisone and ACHROMYCIN® were administered, and supportive therapy was used. When the child was dismissed on the twenty-second day, she was improved but there still was evidence of lye burns of the pharynx, and a gluteal abscess was present.

Case 2—A nonwhite boy, aged two and a half years, picked up some moth balls which had fallen from the pocket of a coat hanging in a closet in his grandmother's apartment, and he put them in his mouth. His temperature increased to 104° F., and he was taken to the hospital four days later. Abdominal pain, nausea, vomiting, pallor, fever and chills were present when the child was admitted to the hospital. The urine was red, and the stools were black. Spectroscopic examination of the blood and urine disclosed breakdown products of naphthalene. Acute hemolytic anemia and oliguria developed, but they were successfully treated with blood transfusions, supportive therapy, alkalinization of the urine, and restriction of the ingestion of fluids. It is interesting to note that ataxia developed on the day on which the child was admitted to the hospital (four days after the ingestion of the moth balls). This subsided slowly. The child was asymptomatic when he was dismissed on the tenth day.

Case 3—A nonwhite boy, aged two and a half years, obtained a bottle of atropine from his grandmother's bedroom while his mother and other members of the family were in another room. He complained of burning in the mouth and throat, and he vomited. He was taken to the hospital. It was difficult to identify the toxic agent because it had been dispensed in a container which bore only the clinic's code number. When the child was admitted to the hospital, his pupils were dilated, and he vomited. A universal antidote was administered, and the child was improved when he was dismissed on the third day.

Case 4—The grandfather of a two year old white boy had had a heart attack and was taking several drugs including morphine sulfate. The child was visiting his grandparents. Prior to his visit, his grandmother had removed all bleaching agents and soap, and had placed all medicines except the cardiac medicines on the top shelves of a medicine cabinet, since she wanted to take every possible precaution to prevent an accident. Unfortunately, both of the grandparents forgot about the cardiac medicines, which were stored in the bedroom. The child was in a crib where he could reach the drawer containing the morphine sulfate. He took the bottle containing the drug, and ingested some of its contents. When the grandmother found the child, he was slumped over the edge of the crib and appeared to be drugged. She realized that he must have swallowed some of the morphine tablets. An emetic was administered immediately, and the child was rushed to the hospital. He vomited on the way to the hospital. His stomach was washed, and an antidote was administered. He was sent home, but he continued to vomit. A physician was called, and he administered phenobarbital. The child was free of symptoms two days later.

Case 5—The mother of a white girl, aged one and a half years, was polishing furniture with Old English scratch furniture polish, and suddenly was distracted by noise from the outside. The child obtained the bottle of polish and drank some of its contents. She did not have any symptoms until evening, when fever developed. The mother called a physician, who told her to induce vomiting. The child subsequently was taken to the hospital. When she was admitted, her temperature was 102.8° F. Her stomach was washed, and penicillin and Achromycin were administered. The child was improved when she was dismissed on the sixth day.

Case 6—The mother of a white girl, aged two years, had left some THORAZINE® pills on a television set. While the mother was sleeping, the child obtained the pills and ingested 15 of them. She became stuporous and comatose, and she was taken to the hospital. Supportive therapy was used, and the child was in good condition when she was dismissed on the fifth day.

Case 7—While playing in the living room of his grandmother, a white boy, aged 22 months, obtained a bottle of PERITRATE® tablets from the top of a television set, and ingested some of them. He did not have any symptoms, but he was taken to the hospital where his stomach was washed. He was dismissed at the end of 24 hours.

Case 8—A three year old white girl was playing with an old pocketbook which contained some DEXEDRINE® sulfate tablets, and she ingested some of them. She became hyperactive, irritable and dyspneic, and she vomited. The mother administered milk immediately, and rushed the child to the hospital. In addition to the above-mentioned symptoms, both pupils were dilated when the child was admitted to the hospital. Phenobarbital was administered, and the child was improved at the time of her dismissal two days later.

Case 9—While a one year old white boy was playing on the floor of the kitchen, he ingested some J-O paste which he obtained from a garbage container. When the child was taken to the hospital, examination disclosed only mild anemia. His stomach was washed, and mineral oil and milk were administered. He was improved when he was dismissed on the fifth day.

Case 10—A four year old white boy climbed up on the washbowl in the bathroom, obtained a bottle of baby aspirin tablets from the medicine cabinet, and ingested 45 of them while his parents were asleep. He complained of abdominal pain and became stuporous. He was rushed to the hospital half an hour after he ingested the tablets. Vomiting was induced, and the stomach was washed. Salicylate was found in the gastric contents and in the urine, but not in the blood. Saline solution was administered, and supportive therapy was used. The child was dismissed at the end of 24 hours.

Case 11—The grandmother of a two year old white girl left a bottle of ROMILAR® (cough) syrup on the dresser and went to the bathroom. The granddaughter obtained the bottle and drank about 2 oz. of its contents. She became stuporous and unable to walk. The grandmother immediately induced vomiting and gave the child raw egg and milk. She then took the child to the hospital, where the stomach was washed. The child was improved when she was dismissed at the end of 24 hours.

Case 12—This case is of particular interest because of the manner in which the poisoning occurred. The mother of a two year old white boy had put a teaspoonful of lye in the washtub, and then had put the empty spoon on the sideboard. The boy picked up the spoon and put it in his mouth. He immediately cried and complained of burning in his mouth and throat. He was taken to the hospital where he remained for 10 days.

Case 13—While visiting a neighbor, a two year old Puerto Rican boy obtained a bottle of Clorox from the ledge of a kitchen window and drank some of its contents. He immediately complained of burning in his mouth and throat, and he was taken to the hospital. His stomach was washed, and supportive treatment was used. He had recovered completely when he was dismissed on the sixth day.

Case 14—An eight year old nonwhite boy had a cough, and his mother wanted to give him some cough medicine, but she unfortunately mistook oil of wintergreen for the cough medicine. Burning occurred in the child's mouth and throat, pain occurred in the abdomen, and nausea developed. The child was taken to the hospital immediately. Vomiting was induced, a universal antidote was administered, and supportive therapy was used. The child recovered completely.

Case 15—The grandmother of a seven year old nonwhite boy wanted to give him some castor oil, but she gave him camphorated oil by mistake. The child became dizzy. The grandmother induced vomiting by putting her

fingers in the boy's throat. He was taken to the hospital, where the stomach was washed and supportive therapy was used. He recovered completely.

Case 16—A two year old nonwhite girl found a bottle of methadone hydrochloride tablets which were being used by her father, who was a drug addict. She ingested three of the tablets. She was admitted to the hospital after initial treatment in the emergency room. She was very stuporous for 12 hours; however, she responded well to an injection of NALLINE® hydrochloride every four hours. The stomach was washed, and artificial respiration was used. She was well when she was dismissed two weeks later.

Cases 17 and 18—While a white mother was polishing shoes with Esquire white shoe polish, she suddenly was distracted by some noise from the outside. Her two year old son obtained the polish and drank some of it. While the mother was scolding the son, her four year old daughter also drank some of the polish. It is believed that both of the children thought that the bottle contained milk. (Fortunately, most white shoe polishes are prepared with white titanium oxide.) The children were taken to a physician, who induced vomiting and sent them home.

Case 19—A pediatrician had been given a sample of SELSUN® sulfide. After he had used some of it as a dandruff remover, he left the remainder on the edge of the bathtub. His 15 month old daughter went into the bathroom and drank some of the Selsun sulfide. The ingestion did not produce any symptoms. The father administered milk as a first-aid measure, and the child apparently recovered completely.

I know of other members of physicians' families who have been poisoned by Selsun sulfide. The bottle containing this preparation has a poison label. It appears, however, that the ingestion of this substance does not constitute a major emergency, primarily because selenium sulfide is insoluble and the preparation contains soap which is a "built-in" emetic.

Case 20—A white boy, aged four years, climbed onto a chair and then onto a washing machine in order to reach the top shelf of a kitchen closet. The shelf was 6 ft. above the floor. He obtained a bottle containing capsules of DEXEDRINE® sulfate, and he ingested all of them. He then gave the empty bottle to a younger sibling. It is believed that the child ingested five capsules, or 60 mg. of the drug. He became excessively talkative, and mania was present when he was admitted to the hospital. Sixty milligrams of phenobarbital was administered intramuscularly. The child had recovered completely when he was dismissed on the third day.

Case 21—A two and a half year old girl climbed up on a chair and obtained Preludin tablets from a shelf in a cabinet. The mother believed that the child put about 15 tablets in a glass of water and then drank the contents. Within a short time, the child became very talkative and excited, and involuntary movement of the hands became evident. An emetic was administered, and the child was taken to the family physician about two hours after she had ingested the tablets. She was talking incessantly, and marked tremors were present. Excitement, tremors and incessant talking still were present when the child was admitted to the hospital. It was necessary to administer ½ gr. of phenobarbital sodium intramuscularly, every four hours for 36 hours, in order to control the excitement completely. The child was dismissed in good condition.

Case 22—A four year old white girl was admitted to the hospital on December 18, 1956, because of coma which had been present for 48 hours. She had been in good health until 3 P.M. on December 16, when she had collapsed after the ingestion of 12 capsules of NEMBUTAL® sodium, each of which contained ¾ gr. of the drug. Her grandmother, who had been preparing to take a trip, had removed the capsules from a medicine chest and had placed them on a table. Unfortunately, the ingestion of the capsules was not detected immediately.

The child was admitted to the hospital. Her stomach was washed, and BENZEDRINE® sulfate was administered. She was placed in a Drinker respirator. An aqueous solution of dextrose was administered intravenously, and

a Foley indwelling catheter was inserted. Antibiotics were administered, and a Levin tube was inserted into the stomach. At 6 A.M. on December 17, she was transferred to Bellevue Hospital in the respirator in an open truck. The respirator was operated manually while the patient was being transferred. When she was admitted to this hospital, she was acutely ill. No pulse could be detected, and the heart beat was not audible. A 1:1000 aqueous solution of ADRENALIN® was administered immediately, and a faint pulse could be felt subsequently. Her skin was cold and clammy, her pupils were widely dilated, and perioral cyanosis was evident. Flaccid paralysis developed, reflexes could not be elicited in any of the extremities, and sensation was absent.

Fluids containing LEVOPHED® bitartrate and antibiotics were administered intravenously. Roentgenographic examination disclosed that the lower lobe of the right lung was collapsed, and bronchoscopy revealed very little secretion. The urinary output was good. She never regained consciousness, and her blood pressure had to be maintained with drugs. At 4 P.M. on December 18, a considerable amount of bronchial secretion became evident, but she died before a tracheotomy could be performed. Postmortem examination revealed "congestion of all organs," and the concentration of barbiturate in the tissues was found to be 1.5 mg. per 100 gm.

Case 23—Another needless death due to barbiturate poisoning occurred in a three and a half year old child who was found staggering and weaving by her mother. About an hour later, the child fell asleep and could not be aroused. Epidemiologic investigation failed to reveal how the child obtained the toxic agent, but it disclosed that barbiturates and other sedatives were in the house. The postmortem examination disclosed that death was due to barbiturate poisoning.

Symptoms and Treatment of Poisoning

The most common symptoms were burning in the mouth and throat, vomiting and stupor. Many of the patients did not have any symptoms. More than 65 per cent of the patients were treated in hospitals. About an equal number were treated in the emergency room and on the inpatient service. About 65 per cent were treated by lavage, either alone or in combination with supportive therapy.

A Poison Control Center Is Established[10,11]

As a result of the stimulating efforts of organized medical groups, the New York City Poison Control Center was established early in 1955. All of the 135 hospitals in the city with emergency and outpatient services are cooperating with the center. The chief reasons for its establishment were to provide physicians with information on the ingredients of substances which frequently cause poisoning, to make diagnostic facilities available, and to recommend appropriate treatment. On the basis of experience gained since the center was established, it is believed that the greatest contribution such a center can make is in the prevention of poisoning. Although the treatment of poisoning is important, the ultimate goal should be its prevention. The New York City Poison Control Center is making information on poisoning available to other similar centers.

A poison control center should obtain epidemiologic data based on field investigation, and should formulate preventive measures based on the data obtained. The information obtained in this manner should be promptly disseminated to other public and private agencies concerned with poisoning. The center also must recommend standardization of dosage, proper labeling and packaging of toxic substances, and other precautionary measures to be employed in homes and industry.

One of the major emergencies encountered by physicians is the ingestion of toxic substances with suicidal intent or the accidental ingestion of massive doses of toxic agents by children. At present, the side reactions of drugs, contraindications to their administration, and the effects of therapeutic doses are discussed by manufacturers of various drugs in professional literature and in directions for use of the respective drugs. The Advisory Committee of the Poison Control Center, therefore, recently made the following recom-

mendation. "Pharmaceutical companies should in their brochures and package circulars to physicians on new drugs describe briefly: the maximum therapeutic dose; the dosage level of serious toxicity, particularly in children; symptoms and signs of massive overdosage; treatment." This recommendation was released to the drug industry, to appropriate professional and trade publications, and to enforcement agencies concerned with drug control.

Prevention of Poisoning

The results of the epidemiologic study on which this paper is based indicate that accidental chemical poisoning of children is preventable if ordinary safety precautions are employed in the handling, use and storage of drugs and toxic household preparations.

Proper labeling of toxic substances is important. The Poison Control Center has been successful in motivating manufacturers of drugs and chemicals to make labeling of their products more effective. The labels on toxic products should contain warnings, in boldface type, for parents to keep the product out of the reach of children. The labels also should contain instructions for the treatment of poisoning caused by the respective products. It is believed, however, that it is unwise to place complete reliance on the label content, since many persons do not read the label, and in most cases the content of the label would not be very meaningful. All safeguards, therefore, must be employed, and every prophylactic measure must be utilized.

Accidental chemical poisoning is due to many causes. Seemingly unrelated factors also may be implicated. The problem is very complex, and involves both human and environmental components. The successful solution of this problem requires the co-ordinated action of physicians, public health workers, pharmacists, engineers, pharmacologists, industrialists, nurses, chemists, sanitary workers, lawyers, housing authorities, law enforcement officers and social workers. Education is very important. Although the task is a formidable one and many gaps still exist in our knowledge, maximal advantage must be taken of the knowledge that is available. The problem could be greatly ameliorated if the available knowledge were more widely utilized.

Role of the family physician—The family physician is most important in the prevention of accidental poisoning. Informing, guiding and counseling families are part of the daily practice of the modern physician. Unfortunately, safety and accident prevention have not yet become part of the average physician's traditional thinking and practice. To fulfill his responsibility as a health adviser to his patients, he must acquire a wider knowledge of safety problems. A useful approach might be the early teaching of the prevention of chemical poisoning in medical schools. Such teaching also might be included in schools of nursing, pharmacy and public health. The teaching should include a visit to a poison control center.

The family physician, because of his intimate knowledge of the biologic and environmental background, customs, traditions and attitude of the families of his patients, has a rare opportunity to inform them about existing hazards in their homes and to motivate them to take the necessary safety measures. He also knows the stage of growth and development of their children and the type of poisoning that is most likely to occur at a given stage of growth and development. He can thus provide the necessary guidance to parents, and this may prevent many needless accidents.

During home visits, or when parents visit his office for health supervision of well children, he can provide guidance about the prevention of chemical poisoning. While in the home, for whatever purpose, he can carefully observe any potential hazard and recommend corrective measures. During office visits, he can advise parents about the development of safe habits and attitudes by their children. He can stress the importance of keeping drugs and household preparations in their original containers and out of the reach of children. He also can advise them regarding the safe storing, care and handling of such preparations. A recommendation to read the label on the preparation also may prove helpful. He

also may give parents and children an opportunity to participate actively in a safety program by giving them a list of safety procedures. His waiting room should include educational material about accidental poisoning. This material should be accurate, simply written, and free of overdramatization. It should be attuned to the educational level of his patients.

The quantity of a drug prescribed should be merely sufficient to meet the immediate needs. The prescription should be written legibly, and the family should be given written directions about the use of the prescription. Adult members of the family should be cautioned to keep toxic drugs out of the reach of children. Parents should be strongly advised against the administration of drugs that have not been prescribed by the physician and against having prescriptions refilled without consulting him.

The physician must adopt safe practices. He should not distribute sample drugs unless they are in their original containers and include careful instructions about dosage, storing and handling. It also is strongly recommended that data about accidents be made a part of the patient's medical record. This will insure the physician's interest in the accident problem. He must look on himself as the poison control officer for his patients and the community in which he lives. He should carry on a self-inspection program such as has been used effectively in food sanitation.

In order to set a good example, he may begin by making a safety survey of conditions in his office, his home, and the hospital in which he works. This survey may reveal many hazards regarding the labeling, storage and handling of drugs, and their accessibility to children in hospitals. Armed with these facts, he can take the necessary precautions which will prevent needless accidents in his own office, and he can make recommendations which will prevent such accidents in hospitals.

He also should orient pharmacists and nurses on the importance of caution and safety when dispensing drugs and other chemical substances. As a civic leader in the community, he can influence attitudes and can motivate community groups such as health councils, parent-teacher associations, Boy Scouts and Girl Scouts to inaugurate safety programs and to practice safety at all times.

Summary and Conclusions

This report is based on an epidemiologic study of 4,469 cases of chemical poisoning which were reported to the New York City Poison Control Center in the first 11 months of 1956. In 2,340 of the 4,469 cases, the patients were less than 19 years of age. Eighteen hundred and five (40 per cent) of the 4,469 patients were less than four years old, and 735 (16 per cent) were in the first two years of life. Children of this age are avid explorers and "mouthers," and their poisoning frequently is the result of exposure of toxic substances in the home of an inexperienced person.

The incidence of poisoning was higher among boys than it was among girls. It was higher among nonwhite children than it was among white children. This most likely is attributable to social and economic conditions, such as poor housing and overcrowding, rather than to any constitutional difference. In many cases, the epidemiologic investigation revealed other accident hazards and public health problems in homes where poisoning occurred.

Drugs intended for internal administration were responsible for the poisoning in 2,421 (54 per cent) of the 4,469 cases. Aspirin was the cause of the poisoning in 567 cases. Household preparations, including bleaching agents and lye, were responsible for the poisoning in 810 cases. In many of these cases, the preparations were not in their original containers and were stored in open utensils on the floor or under the kitchen sink. This indicates that there is a close relationship between the availability of toxic substances and the incidence of chemical poisoning.

Lead was reported as the cause of the poisoning in 111 cases. In 103 of these cases, the patients were less than 19 years old. Ninety-four cases were confirmed at the time of this writing. In 73 (77 per cent) of the 94 confirmed cases, the children were Negroes or Puerto Ricans. There was no significant dif-

ference in the incidence of this type of poisoning according to sex, although it occurred far more frequently in white girls than it did in white boys. In 72 (77 per cent) of the 94 cases, the poisoning occurred in children who were in the first three years of life. The epidemiologic investigation usually revealed that the affected children had chewed flaked plaster or paint peelings.

Chemical poisoning of children is preventable if ordinary safety precautions are employed in the handling, use and storage of drugs and toxic household preparations. Toxic substances should be labeled properly. Education is most important in the prevention of chemical poisoning. Since the family physician has intimate knowledge of the biologic and environmental background of the families of his patients, he has an excellent opportunity to inform them about existing hazards in their homes and to encourage them to take the necessary safety precautions.

I am grateful to Mr. Harry W. Raybin, Technical Director of the Poison Control Center, for many valuable suggestions; to Dr. Morris Greenberg of the Bureau of Preventable Diseases; to Miss Florence Rich for aid in compiling the statistical data, and to many public health nurses for their invaluable aid in the field investigation.

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Books Received

Books received are acknowledged, and, as space permits, those of principal interest to our readers are reviewed more extensively. Reviews appear in this issue starting on page A-104; additional listings are on pages 210, 232 and A-112.

Halsted of Johns Hopkins; the Man and His Men. By Samuel James Crowe, M.D., Professor Emeritus of Laryngology and Otology, The Johns Hopkins University, Baltimore. 247 pages, illustrated. 1957, Charles C Thomas, Springfield, Illinois. $5.00.

An Atlas of Muscle Pathology in Neuromuscular Diseases. By J. Godwin Greenfield, M.D., G. Milton Shy, M.D., Ellsworth C. Alvord, Jr., M.D. and Leonard Berg, M.D., Department of Health, Education and Welfare; Public Health Service; National Institutes of Health, and National Institute of Neurological Diseases and Blindness, Bethesda. 104 pages, illustrated. 1957, E. & S. Livingstone Ltd., Edinburgh and London. Distributed by The Williams & Wilkins Company, Baltimore. $9.00.

Essentials of Clinical Proctology. By Manuel G. Spiesman, M.D., Associate Professor of Proctology, and Louis Malow, M.D., Associate in Surgery, Chicago Medical School, Chicago. Ed. 3. 316 pages with 129 figures. 1957, Grune & Stratton, Inc., New York and London. $8.75.

Treatment of Burns. By Curtis P. Artz, M.D., Associate Professor of Surgery, University of Mississippi Medical Center, Jackson, Mississippi, and Eric Reiss, M.D., American Cancer Society Scholar and Instructor in Medicine, Washington University School of Medicine, St. Louis. 250 pages with 105 figures. 1957, W. B. Saunders Company, Philadelphia and London. $7.50.

Regulation and Mode of Action of Thyroid Hormones. Ciba Foundation Colloquia on Endocrinology. Edited by G. E. W. Wolstenholme, O.B.E., and Elaine C. P. Millar, A.H.-W.C. Vol. 10. 311 pages with 114 illustrations. 1957, Little, Brown & Company, Boston. $8.50.

Fluid and Electrolytes in Practice. By Harry Statland, M.D., Associate in Medicine, University of Kansas School of Medicine, Kansas City, Kansas. Ed. 2. 229 pages, illustrated. 1957. J. B. Lippincott Company, Philadelphia and Montreal. $6.00.

A Manual of Human Anatomy; Abdomen and Pelvis. By J. T. Aitken, M.D., Reader in Anatomy, University College; G. Causey, F.R.C.S., Sir William Collins Professor of Anatomy, Royal College of Surgeons, London; J. Joseph, M.D., Reader in Anatomy, Guy's Hospital Medical School, London, and J. Z. Young, F.R.S., Professor of Anatomy, University College, London. Vol. III. 135 pages, illustrated. 1957, E. & S. Livingstone Ltd., Edinburgh and London. Distributed by The Williams & Wilkins Company, Baltimore. $3.50.

Reading Disorders

E. GILLET KETCHUM*

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E. GILLET KETCHUM

In this country over four million school-age children of average or better intelligence are experiencing specific difficulty in various areas of learning. These children represent approximately 10 per cent of the school population. Retardation in acquiring the skills of reading clearly leads this field, and the ratio of boys to girls presenting this disorder is six to one. This dysfunction is by no means confined to the United States alone, as UNESCO studies reveal a similarly high incidence of such anomalies in the Scandinavian and European countries. Despite widespread and intensive research, it is a syndrome which still commands much etiologic controversy.

Learning to read is not the simple task it once was thought to be. It is not just a matter of "look and learn," of an automatic transition from perception to conception. From an ontogenetic viewpoint, reading is the latest of man's functional accomplishments in the abstract. Yet the general attitude toward learning to read is one which too often assumes a casual expectancy of success in this extremely complicated undertaking.

Reading consists, first, of several primary skills. Mastery of the "mechanics" is fundamental. Herein is required facility in visual perception of form, of spatial orientation, and of the spatial and temporal sequences of letter orders. Secondly, except in the congenitally deaf, the reading function is rendered more efficient by the child's skill in the association of sounds with letters and vice versa. It is in the field of these initial skills that a majority of the reading problems, particularly the early ones, arise. Perceptual confusions, such as "was" for *saw*, "raddit" for *rabbit*, or "post" for *stop*, appear frequently in the initial learning phase. In earlier days these faulty perceptions were termed "strephosymbolia," or "mirror vision." Phonic errors, such as "toe" for *to*, "kitty" for *city*, are often prevalent until appropriate training has been given. Both types of errors may often appear in spelling. In the very early learning stages, these errors

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are not unusual, but, when they persist, they are symptomatic and, therefore, indicate a need for inquiry.

If symbols are properly perceived and grouped, the meaning of the word, if it is in the child's experience, can become clear. From here, integration of words into meaningful units and ideas is achieved. In reading problems appearing at this stage, ideational errors can prevail. These consist of omission of words from the sentence, substitutions such as "boat" for *ship* and "mule" for *donkey*, or additions of words not in the context. Such error patterns suggest that the child may have become an expert at guessing, or is merely "calling words"; he may be just "going through the motions" of reading while comprehending little. In this second phase of learning to read, these error patterns usually have psychologic origins.

Difficulties in the "mechanics" of reading may on investigation prove to be a concomitant of intellectual retardation. In the normally intelligent child, adverse environmental influences, insufficient preparation for reading, or poor teaching may play a part. Faulty vision is of course inimical, but it does not by any means play a major role. Our studies show an increasing number of children presenting generalized cortical dysfunction as a contribution to reading disorder. In the majority of our cases, however, primary, *not* secondary, personality problems appear to have the highest causative incidence. It is rare not to find that some combination of these factors is etiologic. There is lessening evidence supporting the theories of Orton that failure to establish unilateral cerebral dominance for language is solely causal. In this latter regard, our data no longer reveal significant learning differences between children of "mixed motor dominance," of left and right preferences for handedness and monocular sighting, and those with unilateral preferences.

Research and experience reveal the following prerequisites for a child's learning to read:

1. Good general health.
2. Adequate background of social and environmental experience.
3. Average or better intelligence.
4. Accurate monocular or binocular vision for the usual reading distance.
5. A cerebral cortex which can efficiently perceive letters and letter orders, and associate their concomitant phonetic values.
6. Personality dynamics which will enable and motivate the child to perceive adequately, and to deal effectively with frustrations and adjustments of individual and group learning situations.
7. Skilled teaching and proper teaching conditions.

Should any one of these interdependent preconditions not prevail, the child will usually experience initial difficulty, if not utter failure, in this vital stage of the learning experience. These conditions are usually prerequisite to most learning success, but they are clearly specific to acquiring the complicated skills of reading.

When through informal or standardized educational tests a youngster is discovered to be well behind his group in achieving reading success, thorough evaluation is certainly indicated. The seven points previously listed also should be considered as the chief criteria for diagnostic study of any child's discovered retardation in reading. No matter whether the child is at the stage of "learning to read," or "reading to learn," whether he is a second grader or in junior high school, these are the factors which must be differentiated if the causes of his difficulty are to be properly diagnosed. To omit or to assign overmuch or only incidental importance to any one element can result in biased diagnosis. It is not infrequently found that treatment of reading disorders based on faulty rationale can be disastrous to the child's future.

If reading disability is accepted as a *syndrome* by all concerned, responsibility for helping a disabled reader can rest with no single authority. Without assurance of the child's general health or of the absence of past or present physiologic anomalies which might contribute, the psychologist or educational specialist may proceed on a wrong course to the detriment of the child. On the other hand, if an experienced and qualified clinician finds evidence in his psychologic investigations

pointing to possible physiologic or neurophysiologic dysfunction, it is certainly no help if the physician summarily dismisses this concept without appropriate evaluation. When such dysfunctions exist either unnoticed or untreated, specially devised re-educational methods imperative in such instances may not be formulated. Moreover, it has been our experience that there are quite a number of children with reading disabilities whose etiologic picture includes neurogenic factors and who may be aided in their response to remedial reading instruction, plus all learning and adjustments in general, by appropriate chemotherapy. This appears particularly true in those children whose neurologic evaluation is clinically negative, but who do have generalized cortical dysrhythmia.

Personality problems are frequently a *primary* cause of reading disorders. Too often deviations in behavior, signs of insecurity, and passive or belligerent attitudes are thought to be a reaction to the student's failure to acquire reading efficiency. Five typical personality patterns are found to cause reading failures:

1. The "too good," overly conforming child, in whose home there predominates a "Mamma knows best" atmosphere.

2. The infantile youngster who has been "spoiled" by too permissive and possessive parents, who avoid the tribulations of their responsibility by keeping the child "enjoyably" babyish.

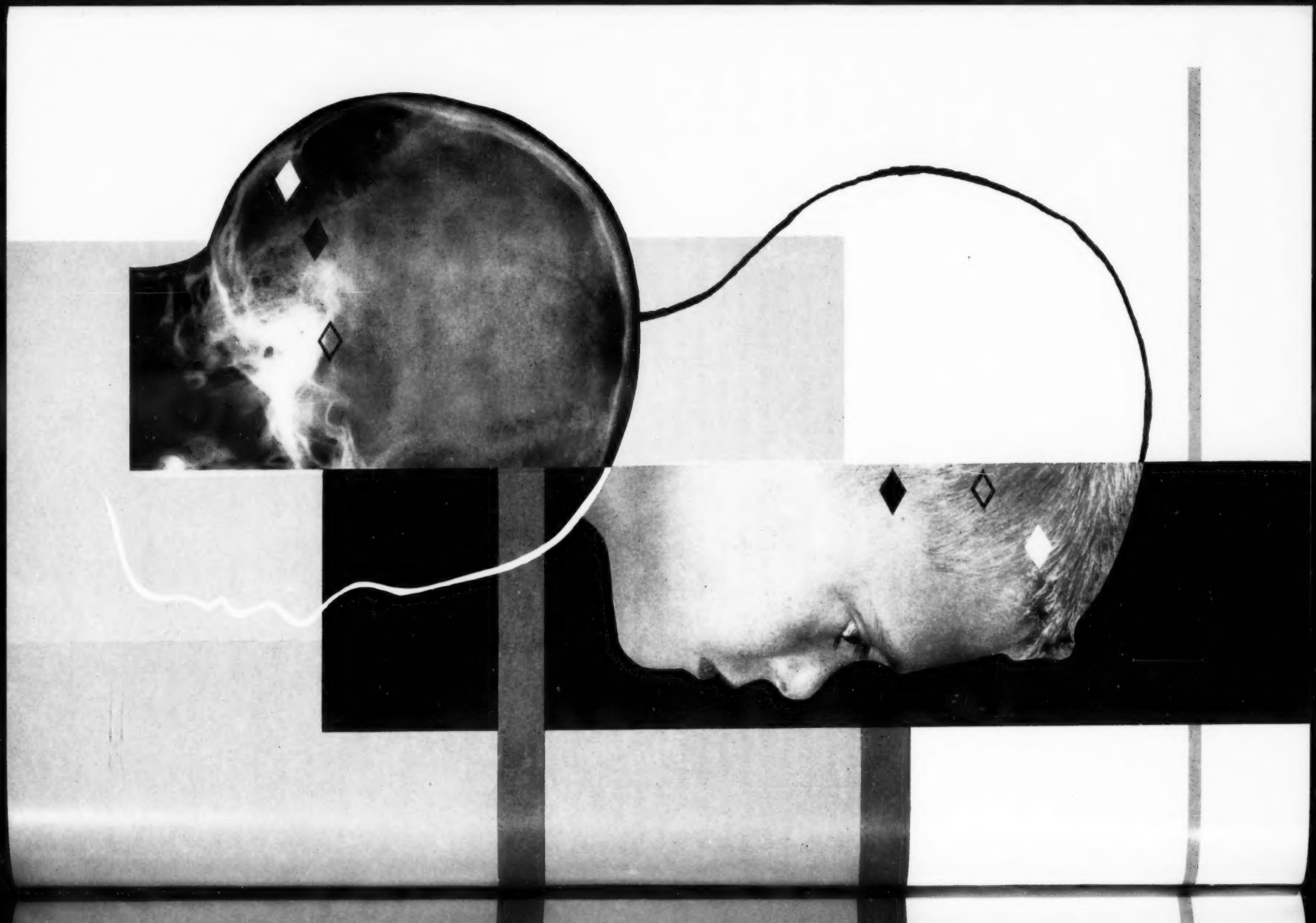
3. The passive, dependent individual who adopts a hedonistic attitude toward all things; he tolerates no frustration, his needs having always been anticipated and fulfilled.

4. The resistive, negativistic youth who pursues his needs for power by fighting parental pressures by refusing to learn.

5. The "I'm dumb" child who has inverted aggressive energy in masochistic fashion and resists learning progress by the face-saving "I want to, but I *can't*" approach.

Limitations of space enforce these oversimplified symptomatic descriptions. Underlying these are usually deeply embedded personality problems often requiring psychiatric evaluation and psychotherapy. Treatment should always include *both* parents.

When a patient is reported to have difficulty in learning, the best course is to obtain as eclectic an evaluation as possible. Do not accept group-administered test scores as a true measure of intelligence, but insist on an individual test such as the Stanford-Binet, or one of the Wechsler scales. Insist, also, on full educational achievement tests so as to secure the child's whole learning pattern. Integrated with these findings should be analysis of the personality factors by projection tests. Thorough evaluation and successful treatment of reading disorders usually require a "team approach," and cooperation and co-ordination among physician, parents, psychologist and educator.



Brain Tumors in Childhood

ROBERT S. KNIGHTON*

Henry Ford Hospital, Detroit

Supratentorial 35%

- Glioma of cerebral hemisphere 15%
- Craniopharyngioma 8%
- Miscellaneous 12%

Glioma of optic chiasm
Papilloma of choroid plexus
Epidermoid, dermoid, teratoma
Lipoma of corpus callosum
Colloid cyst of third ventricle
Meningioma

Infratentorial 65%

- Cerebellar astrocytoma . . 25%
- Medulloblastoma 17%
- Ependymoma 11%
- Glioma of brain stem . . . 7%
- Miscellaneous 5%

SYMPTOMS AND SIGNS

Headache
Vomiting
Diplopia
Unsteadiness of gait
Progressive loss of vision
Papilledema
Cranial nerve palsies
Head tilting and stiffness of neck
Nystagmus
Convulsive seizures
Hemiplegia and spasticity

DIAGNOSIS

History and neurologic examination
Skull x-ray
- Calcifications
- Separation of suture lines
- Accentuation of convolutional markings
- Erosion of clinoid processes
- Enlargement of optic foramen

Electro-encephalography
Ventriculography
Arteriography

TREATMENT

Surgical removal
Radiation therapy
Ventriculostomy
Ventriculocisternostomy (Torkildsen)

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Supratentorial Tumors

GLIOMA OF HEMISPHERES

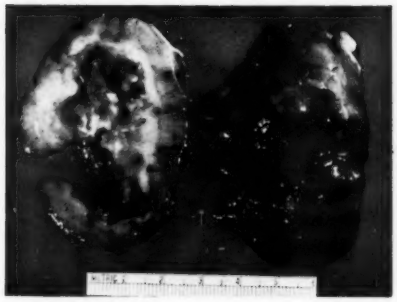
Most common supratentorial tumors, various types, usually malignant

Symptoms and Signs
- Headache
- Cerebral seizures
- Hemiparesis
- Behavioral changes
- Pressure signs

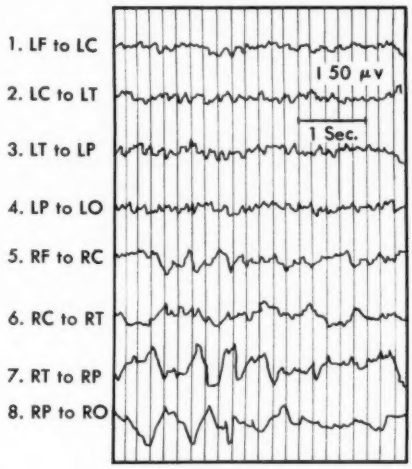
Diagnostic Studies
- X-rays of skull
- Electro-encephalogram
- Ventriculography or arteriography

Treatment
- Surgical excision

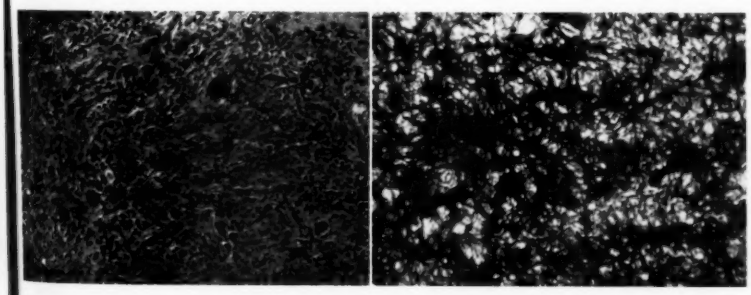
Radiation therapy



Surgical specimen. Gross removal of glioblastoma from right parieto-occipital lobe.



Electro-encephalogram showing delta focus in right parieto-occipital lobe.

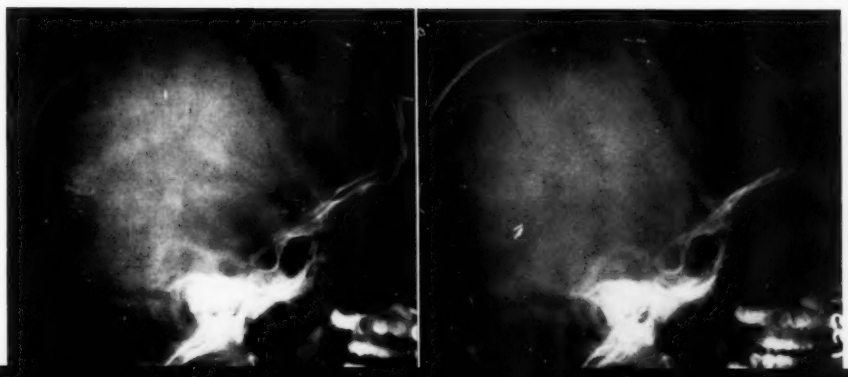


Glioblastoma. This is a very cellular pleomorphic neoplasm with numerous multinuclear giant glial cells and mitotic figures. (Hematoxylin-eosin, x 300.)

Glioblastoma. The same tumor stained by Hortega's silver carbonate (x 300).

Calcification in tumor of parieto-occipital lobe. Suture lines separated from pressure.

Postoperative film shows absence of calcification and closing of suture lines.



Craniopharyngioma. Characteristic arrangement: stratified squamous epithelium, cystic formations, keratin pearls. (Hematoxylin-eosin, x 200.)

CRANIOPHARYNGIOMA

Congenital tumor derived from cell rests of buccal pouch

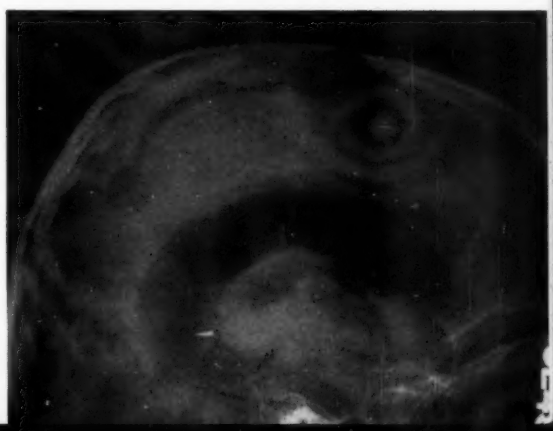
Symptoms and Signs
- Hypothalamic
  - Diabetes insipidus
  - Primary hypogonadism
- Endocrine
  - Hypopituitarism
- Visual
  - Visual field changes
  - Optic atrophy
- Increased intracranial pressure
  - Due to block at interventricular foramen of Monro

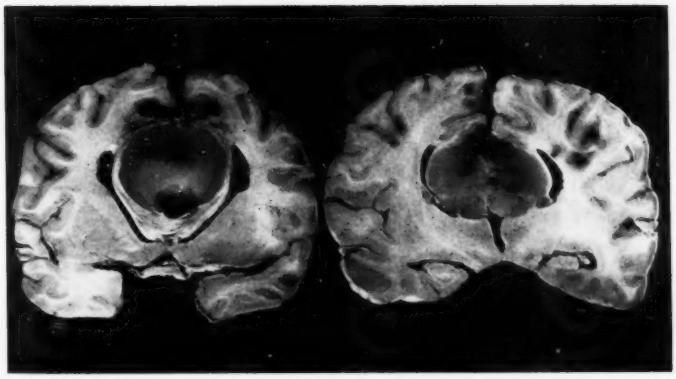
Diagnostic Studies
- Studies of endocrine and hypothalamic function
- X-ray (70% calcified)
- Pressure changes about sella
- Arteriography or ventriculography

Treatment
- Surgical excision (25%)
- Ventriculocisternostomy (Torkildsen)
- Endocrine replacement

X-ray of pituitary fossa showing intracellular calcification and erosion of posterior clinoid process.

Ventriculogram showing elevation of floor of third ventricle by cyst.





Lipoma of the corpus callosum with irregular extension of the lipoma into the brain. Narrowing and lateral displacement of lateral ventricles.

LIPOMA OF CORPUS CALLOSUM

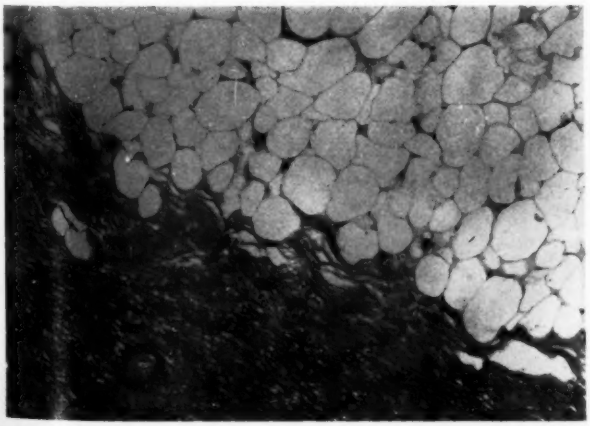
Rare, congenital, mid-line lesion

Symptoms and Signs
- Headache
- "Blackout" spells, or convulsions
- Papilledema

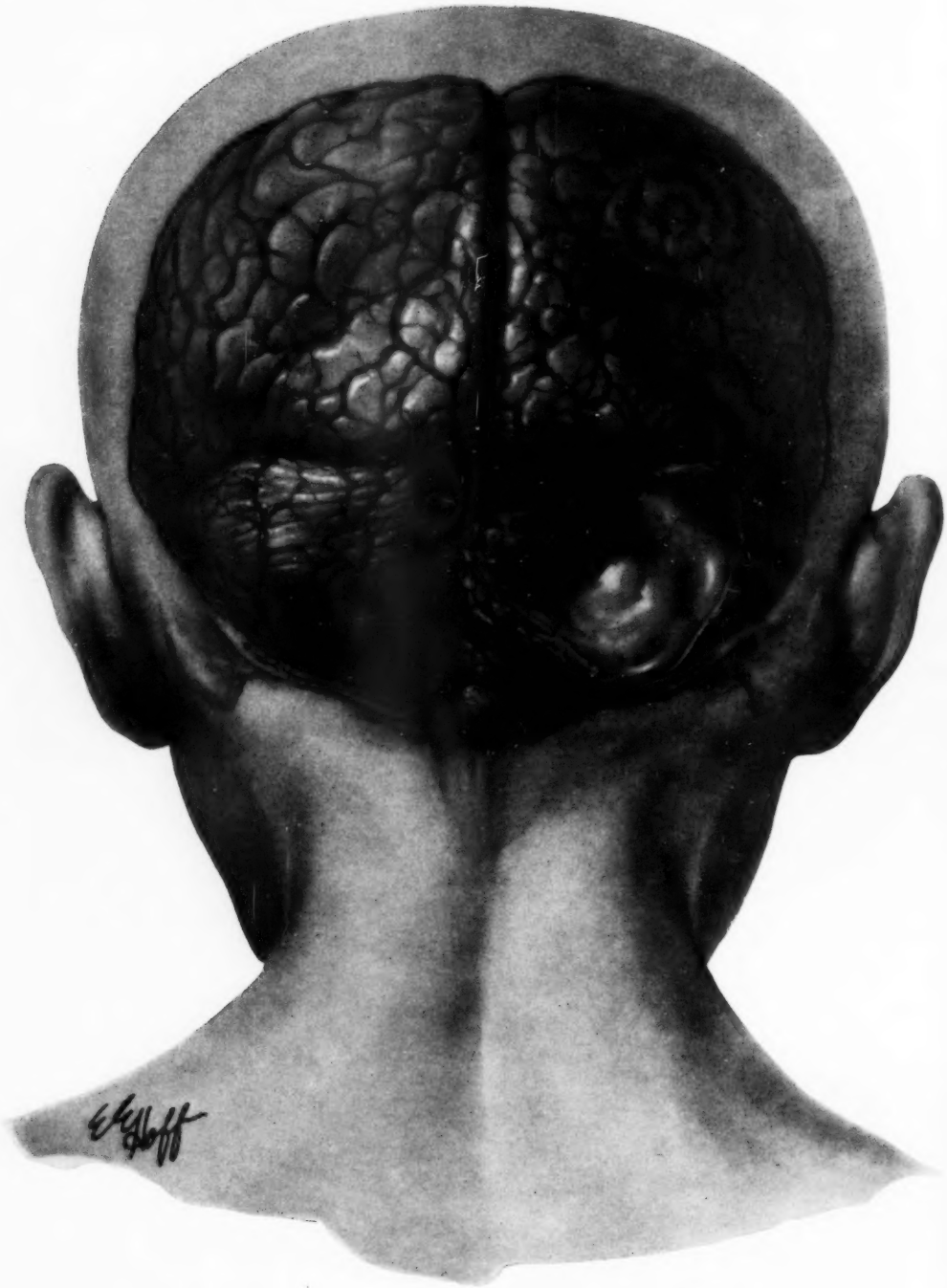
Diagnostic Studies
- Electro-encephalogram
- X-ray of skull
- Ventriculography or arteriography

Treatment
- Ventriculocisternostomy
- Surgical removal if above is not adequate

Lateral ventricles separated by tumor of corpus callosum.



Lipoma of corpus callosum. Section of the corpus callosum with the attached lipoma composed of adult fat cells. (Hematoxylin-eosin, x 70.)



Infratentorial Tumors

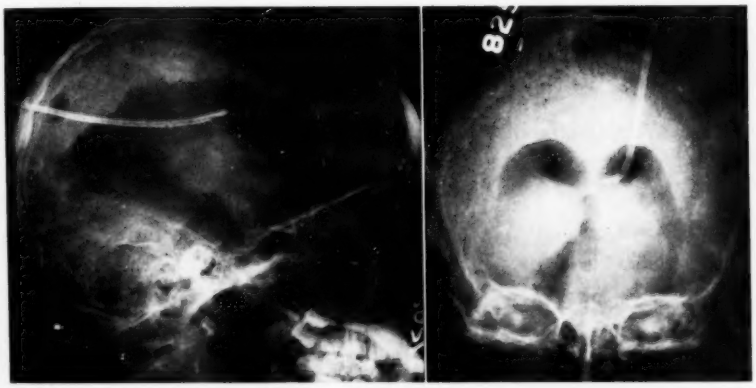
ASTROCYTOMA OF CEREBELLUM

Most common, benign, often cystic, often hemispherical

Symptoms and Signs
- Headache
- Vomiting
- Hypotonia, dysmetria, intention tremor, adiadochokinesia, rebound
- Nystagmus
- Papilledema

Diagnostic Studies
- X-ray of skull
- Ventriculogram

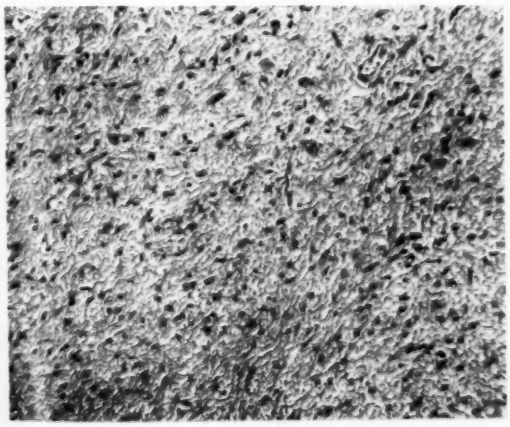
Treatment
- Surgical excision



Enlarged lateral ventricles from posterior fossa tumor. The enlargement and thinning of posterior fossa suggest slow-growing benign tumor.

Dilatation of ventricular system and shift of fourth ventricle and aqueduct due to the hemispheral tumor.

Astrocytoma of cerebellum. Within a feltwork of gliofibrils there are numerous evenly distributed astrocytes. (Hematoxylin-eosin, x 300.)



Astrocytoma of cerebellum stained by Hortega's silver carbonate (x 300).

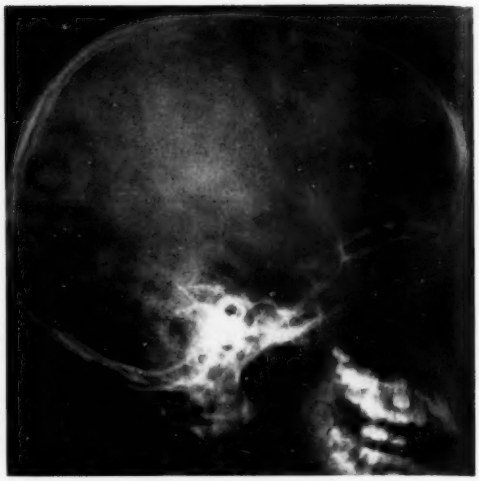
MEDULLOBLASTOMA

Malignant, mid-line cerebellar, short history, "seed" throughout subarachnoid space

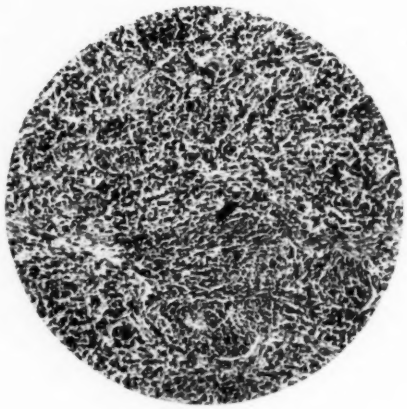
Symptoms and Signs
- Occipital headache and "stiff neck"
- Vomiting
- Tiredness and irritability
- Staggering gait
- Papilledema

Diagnostic Studies
- X-ray of skull
- Ventriculogram

Treatment
- Suboccipital craniectomy, gross removal of tumor and unblocking of fourth ventricle
- Ventriculocisternostomy
- Radiation therapy to entire cerebrospinal axis

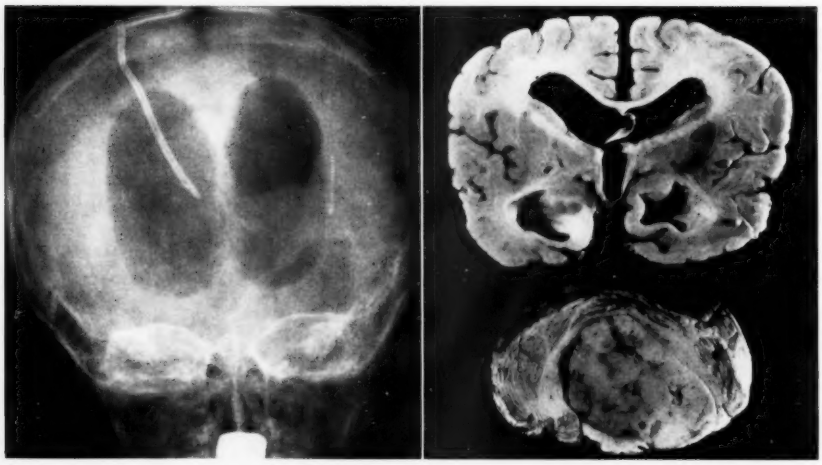


Separation of suture lines due to pressure. Small posterior fossa suggests rapid increase of pressure by rapidly growing tumor.

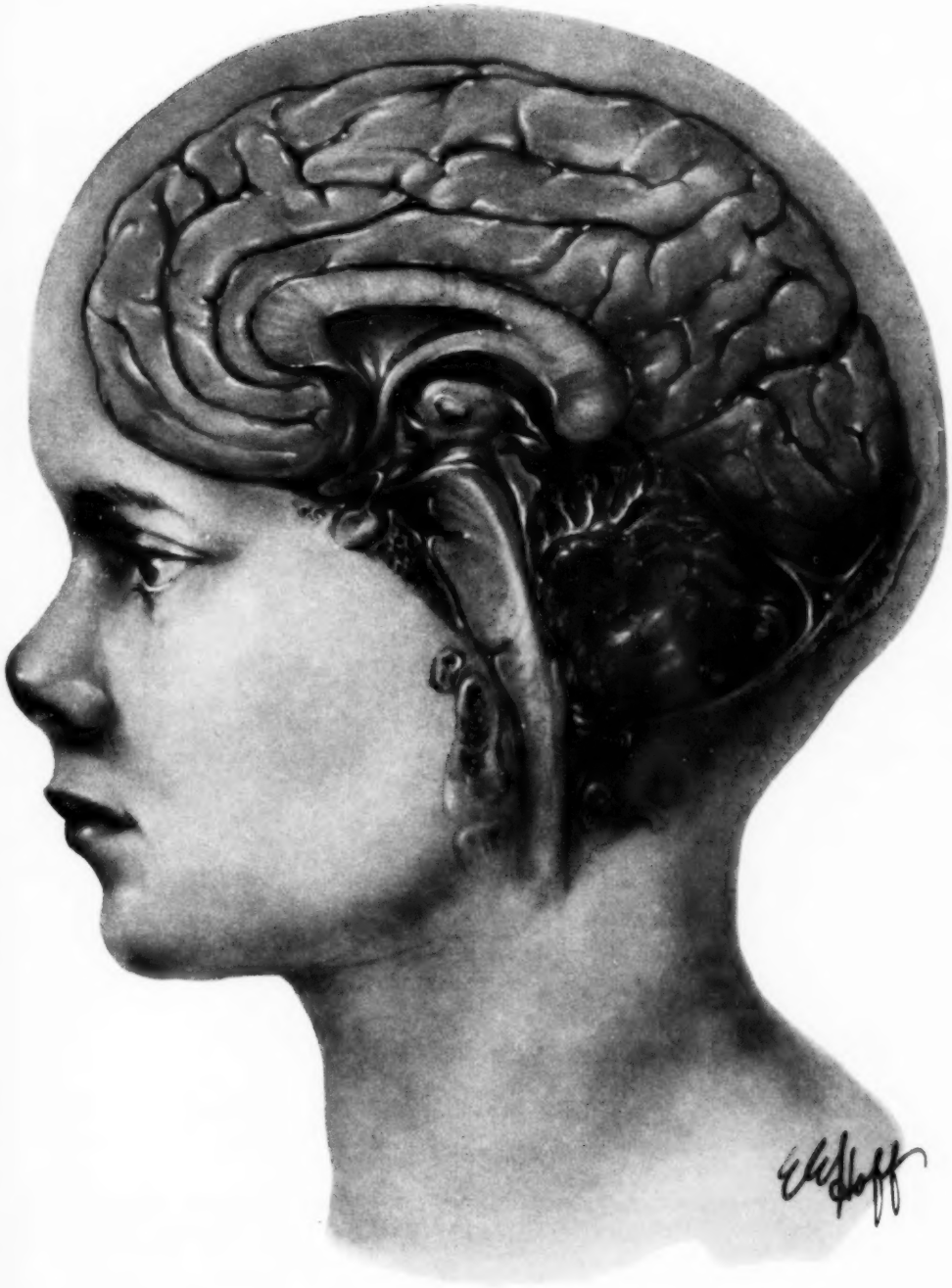


Medulloblastoma. Masses of deeply stained small cells with scanty cytoplasm. There is little stroma and frequent mitoses are present. (Hematoxylin-eosin. x 150.)

Symmetric dilatation of ventricular system due to block of aqueduct of Sylvius by tumor.



Medulloblastoma of vermis and fourth ventricle. Hydrocephalus due to block of aqueduct of Sylvius.



GLIOMA OF BRAIN STEM

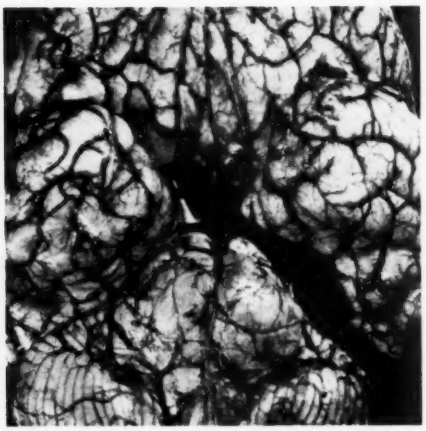
Cranial nerve palsies early, pressure signs late or never

Symptoms and Signs
- Cranial nerve palsies
  - Trigeminal
  - Abducens
  - Facial
  - Other
- Paraparesis and spasticity
- Pressure signs late or never

Diagnostic Studies
- Clinical examination
- Pneumoencephalogram

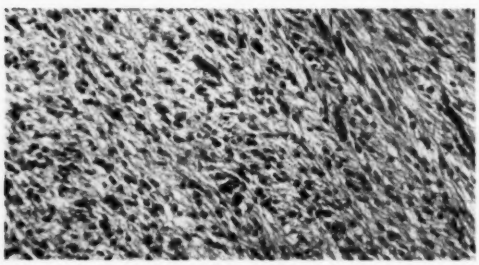
Treatment
- Radiation therapy

Elevation of floor of fourth ventricle by glioma of pons.

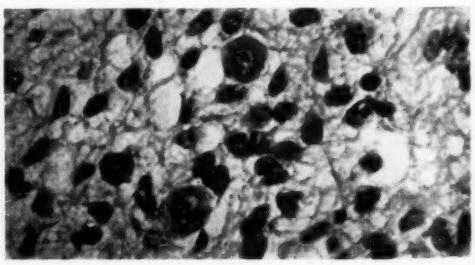


"Pseudohypertrophy" of the pons due to a diffuse glioma of the brain stem.

Spongioblastoma of pons showing parallel arrangement of tumor cells.



Same tumor showing well-preserved neurons within tumor. (Hematoxylin-eosin, x 200.)



Hemolytic Anemias in Childhood

WOLF W. ZUELZER*

Wayne University College of Medicine, Detroit

WOLF W. ZUELZER

THE common denominator of all types of hemolytic anemias is the shortening of the life span of the erythrocytes. There are other conditions, such as pernicious anemia, in which some degree of hemolysis is associated with primary disturbances in the production of erythrocytes by the marrow organ; but, customarily, the designation "hemolytic anemia" is restricted to those conditions in which increased destruction of the red corpuscles is regarded as the basic abnormality.

Generally it is possible to distinguish between two kinds of hemolytic anemias: those in which an intrinsic defect in the structure of the erythrocytes renders them more vulnerable to the hazards and stresses inherent in a normal environment, and those in which normally formed erythrocytes are damaged in the circulation by a variety of noxious factors. The former group includes intrinsic or intracorpuscular defects and comprises the congenital, inherited abnormalities of the red cell such as congenital spherocytosis, sickle cell disease and other genetically determined anemias. The latter group includes such extrinsic mechanisms acting on the erythrocytes as isoantibodies and auto-antibodies and toxic substances of endogenous or exogenous nature.

*The Child Research Center of Michigan; The Children's Hospital of Michigan, and Wayne University College of Medicine, Detroit, Michigan.

General Features

The normal life span of the red corpuscle is 100 to 120 days. Under ordinary conditions the number of erythrocytes per unit volume of blood, as well as the total blood volume and the oxygen requirements of the organism, remain constant. It follows that in the normal adult the bone marrow organ replaces senescent erythrocytes at the approximate rate of 1 per cent a day, and this rate is reflected in the normal reticulocyte count of about 1 per cent.

When the survival of the erythrocytes is shortened, the rate of production of new cells must be increased if equilibrium is to be maintained. The normally functioning marrow organ has considerable reserve power and is able to increase its output of erythroid cells. The result is erythroid hyperplasia within the hematopoietically active marrow, evident in a decrease of the ratio of myeloid to erythroid cells; a "left shift," i.e., increase in the proportion of young precursor cells and, in the

circulating blood, an increase in the number of erythrocytes. As long as the bone marrow can keep pace with the rate of destruction of the erythrocytes, the hemolytic process remains compensated. There is no anemia but the hemolysis is reflected by reticulocytosis. Frank anemia results only when the rate of hemolysis exceeds the compensatory capacity of the marrow.

In severe and long-standing hemolytic anemias the active marrow extends to sites ordinarily occupied by fatty marrow. The marrow hypertrophy may even lead to widening of the marrow cavities of the long bones and to thickening of the diploë of the skull. Extramedullary hematopoiesis may provide additional capacity for red cell production. In childhood, especially in the first few years of life, when there is little if any fatty marrow at whose expense hematopoiesis can expand, extramedullary blood formation and changes in the bony structures are relatively common in long-standing hemolytic anemias.

The peripheral blood may show, in addition to reticulocytes, nucleated red blood cells and, often, especially in acute hemolytic episodes, leukocytosis and increased numbers of platelets. At times, however, reticulocytosis may be absent and the marrow itself may not show the erythroid hyperplasia ordinarily seen in hemolytic anemias. This is true when the patient undergoes a so-called aplastic crisis or acute erythroblastopenia. At such times, as indicated by these terms, the erythroid activity of the marrow fails more or less abruptly, usually as the apparent sequela of infection. Such an event is very dramatic and of serious import, because the greatly shortened life span of the red corpuscles in hemolytic anemia demands maximal regeneration. The sudden and virtually total failure of erythropoiesis leads to a catastrophic fall in the level of circulating red corpuscles and hemoglobin. Moreover, the diagnosis of hemolytic anemia is difficult to establish at such times.

The red cells show shape anomalies in many hemolytic anemias, both congenital and acquired. Sphering is seen not only in congenital spherocytosis (familial hemolytic icterus), but also in a number of acquired anemias, notably those of auto-immune or iso-immune character. The phenomenon of spherocytosis is associated with an increase in the osmotic fragility of the erythrocytes. In a number of toxic anemias, gross disturbances and shape anomalies of the red cells are found. In sickle cell anemia is seen the characteristic shape anomaly which gives the disease its name.

The increased destruction of erythrocytes must inevitably be accompanied by increased formation of pigment derived from the breakdown of hemoglobin. If hemolysis is massive and intravascular, hemoglobinemia and hemoglobinuria result. If the rate of hemolysis is slower but exceeding the capacity of the liver to excrete the bilirubin formed in the process, hyperbilirubinemia and clinical jaundice are observed. These features are particularly striking in the hemolytic anemias of the newborn because of the notorious inefficiency of the neonatal liver in excreting bilirubin. Regardless of hepatic factors, the stool urobilinogen generally is increased when the rate of hemolysis is elevated. The total quantity of stool urobilinogen is related to the total amount of hemoglobin which is undergoing destruction. It is therefore much smaller in a child than in an adult with a comparable *rate* of hemolysis. In practice it is seldom necessary or useful to resort to a determination of stool pigments to conclude that one is dealing with a hemolytic mechanism. Usually there are other clear-cut signs of such a process when hemolysis is marked. When it is slight or questionable, difficulties in collection and inaccuracies of the method limit its usefulness in pediatrics.

Studies of red cell survival are not a routine tool but have contributed enormously to the present-day understanding of hemolytic mechanisms; they have reached considerable precision and, in selected cases, may be of great value. Generally, whether determined by the Ashby method of differential agglutination or by the method of tagging the erythrocytes with Cr^{51}, intrinsic erythrocyte defects are associated with a shortening of the life span of the patient's red cells in his own circulation as well as in that of a normal recipient, while normal donor cells have a normal life span in the patient's system. By contrast, in acquired hemo-

lytic anemias in which extrinsic factors act on normally formed erythrocytes, donor cells are more or less rapidly destroyed in the patient's circulation. The patient's cells may or may not survive in a normal recipient, depending on whether or not the cells have been irreversibly damaged.

From the information given thus far, essential laboratory diagnostic procedures in hemolytic anemias may be listed as:

1. Morphologic: examination of the red corpuscles by count, hematocrit, hemoglobin determination, stained smear and reticulocyte count. Occasionally, bone marrow aspiration is essential.

2. Serologic: the determination of iso-antibodies and possibly auto-antibodies by suitable tests. Among these, the direct Coombs test, which, properly performed, indicates coating of the erythrocytes with antibody, and the indirect Coombs test, which indicates the presence of free antibody of varying specificity and thermal range in the serum, are basic. There are many additional methods, for which the reader is referred to standard texts, notably Dacie's[1] monograph on hemolytic anemias.

3. Chemical: determination of plasma bilirubin and, if indicated, other plasma pigments; electrophoretic studies for the characterization of abnormal hemoglobin variants. In certain cases toxicologic studies may be indicated.

It is obvious that a good history and family history, as well as physical examination, are at least as important as any of the laboratory procedures which can be devised.

Hemolytic Anemias Caused by Intrinsic Defects

Congenital spherocytosis—This condition is characterized by a shape anomaly of the erythrocytes which, in typical cases, makes them appear as small, round, deeply staining cells in smears; it is associated with increased osmotic fragility. The spherical erythrocytes are vulnerable to destruction in the spleen, which greatly shortens their life span.

Congenital spherocytosis is hereditary and is transmitted like a mendelian dominant. The expressivity of this trait is highly variable and it is not unusual to find its hematologic stigmata in a parent or sibling who is clinically well and has no significant degree of anemia. On the other hand, in many cases the defect cannot be demonstrated in either parent, suggesting that the penetrance of the gene is far from complete.

The clinical picture is variable. Occasionally, profound anemia and jaundice at birth simulate hemolytic disease of the newborn. At later ages there are usually intermittent jaundice, a minor degree of anemia with reticulosis, splenomegaly and, often, some degree of hepatic enlargement. Cholelithiasis occurs in children but it is not common. We have been impressed with the frequency with which migrainelike episodes occur in the patients and in the families.

The severity of congenital spherocytosis being variable, treatment cannot be uniform. Mild cases in which only the stigmata and, perhaps, splenic enlargement are found but in which anemia is absent or minimal and does not interfere with growth, development and cardiac function require no therapy. On the other hand, a crisis, whether it be aplastic or truly hemolytic, is a threatening event. In cases in which a crisis has occurred, splenectomy is indicated, as it is when a significant degree of anemia is present. Splenectomy is virtually specific and nearly always successful when the proper diagnosis has been made. Although the red corpuscles continue to be abnormal, removal of the spleen does away with the trapping mechanism, which is an essential factor in their shortened survival.

Once the indication is established, the timing of a splenectomy is an important point. Though the evidence is by no means conclusive, there are suggestive cases in the literature which indicate that splenectomy in infants may be followed by susceptibility to overwhelming infections such as meningococcemia and pneumococcemia. In my own experience this has occurred only once in many splenectomies performed in the pediatric age group. This was in an infant whose spleen was removed because of severe congenital spherocytosis at nine months of age. During the second year of life this child had two separate episodes resembling the so-called Water-

house-Friderichsen syndrome, which she survived only by administration of the most strenuous therapy. However, Smith and associates[2] reported a sizable series of similar accidents among their patients after splenectomy.

It is our feeling that splenectomy can nearly always be deferred until the third or fourth year, provided the patient can be watched and adequately treated in case of a crisis. The management of a crisis is essentially symptomatic and requires blood transfusions and, in case of infections, suitable antibiotic therapy.

Sickle cell disease—It is now well established that the presence of an abnormal gene, generally referred to as the sickling gene, leads to the production of an abnormal hemoglobin: sickle hemoglobin, the reduced form of which is highly insoluble. Erythrocytes with sickle hemoglobin assume the characteristic shape anomaly of the sickle cell when the hemoglobin is reduced. A single abnormal gene for sickling, paired with a normal gene for the production of normal hemoglobin (hemoglobin A), leads to the asymptomatic sickle trait. In this condition both hemoglobin A and S are simultaneously produced, the concentration of S being somewhere between 20 and 45 per cent. The genotype is AS. Cells containing less than 50 per cent hemoglobin S do not sickle readily in vivo and persons who have such cells are free of hemolytic anemia.

In homozygotes, for the gene leading to production of hemoglobin S, no hemoglobin A is produced. There may be some fetal (alkali-resistant) hemoglobin present, but 80 to 100 per cent of the erythrocyte hemoglobin is the insoluble sickle cell hemoglobin; in such individuals intravascular sickling occurs readily. The life span of these cells is greatly shortened and anemia is usually marked. The intravascular sickling is thought to be responsible for the many symptoms of sickle cell anemia (as the homozygous state is now called). These symptoms arise from stasis of sickled erythrocytes with vascular obstruction and, at times, thrombosis. Such phenomena explain the frequent pain crises, destructive lesions in the skeletal system, ischemic lesions in the central nervous system, and other findings.

In addition, patients with sickle cell anemia are subject to aplastic crises and also to true hemolytic crises. The diagnosis depends on the demonstration of a hemolytic anemia with sickling, the presence of hemoglobin S in the absence of A, and the genetic analysis of the family if possible.

Therapy is largely palliative. If a simultaneous iron deficiency state can be shown to exist, as is not uncommon in infants, it should be corrected. Otherwise the administration of iron is useless. The steroid hormones seem to have no place in the therapy of sickle cell anemia. Transfusions are indicated in case of aplastic or true hemolytic crises, in case of complicating infections, and, perhaps, to bolster growth and circulation in severe cases from time to time. Attempts to keep the hemoglobin at normal levels by continuous transfusion therapy are not recommended, if only because of the hazards of multiple transfusions.

Splenectomy is seldom necessary in an older patient whose spleen shrinks after numerous episodes of infarction. However, in my clinic, infants with early onset of symptoms, severe anemia, very large spleens, and repeated crises have been splenectomized with gratifying results. In four such cases there were no further hematologic crises and the hemoglobin became stable at a higher level although pain crises continued to occur.

The generic term sickle cell disease now includes combination forms in which the sickling gene in single dose is combined with another abnormal gene; for example, that for hemoglobin C or that for thalassemia.

Sickle cell-hemoglobin C disease differs from classic sickle cell anemia by a much milder course, less evidence of hemolysis, fewer if any crises, generally less pain, higher hemoglobin levels, and usually a marked degree of splenic enlargement which, unlike that in sickle cell anemia, does not recede. The genetic background of these patients is SC; on electrophoresis the hemoglobin is composed of sickle and hemoglobin C in the approximate proportion of 50:50, and the smear shows marked target cell formation. The prognosis is considerably better than that of sickle cell anemia. Therapy is not usually required.

Sickle cell-thalassemia disease is a combina-

tion in which the two genes indicated by the name appear to interact in such a manner that each enhances the effect of the other. In single dose, paired with a normal gene, neither the sickle nor the thalassemia gene ordinarily produces gross disease. In the double heterozygotes with sickle cell-thalassemia disease, the production of hemoglobin S is greatly increased, amounting to 70 to 100 per cent of the total. Sickling occurs readily, and, perhaps as a consequence, many such patients have a disease which is clinically indistinguishable from sickle cell anemia. Morphologically, microcythemia and poikilocytosis reminiscent of thalassemia, together with the sickling of the erythrocytes, are the characteristic features. Clinically, the presence of marked and often persistent splenomegaly is suggestive of sickle cell-thalassemia disease. While sickle cell anemia is prevalent in Negroes, sickle cell-thalassemia occurs with appreciable frequency in Caucasians of Greek and Italian descent.

In recent years a number of other combination diseases and hemoglobinopathies have been described. The reader is referred to several monographs dealing with this interesting group of hemolytic anemias.[3-6]

Anemias Resulting From Extrinsic Factors

Two large categories can be distinguished in this group: those in which an immune mechanism can be demonstrated, and all others. In the former group, by far the most important conditions are Rh and ABO hemolytic disease of the newborn. However, so-called acquired auto-immune hemolytic anemias are not uncommon in later infancy and childhood.

Hemolytic disease of the newborn—There is now abundant information available on classic Rh hemolytic disease and only a few points need to be stressed here. The diagnosis should be established, at least tentatively, in the prenatal period. It is the usual custom in many parts of the country to check the serum of an Rh-negative woman for Rh antibodies only during the second (or any subsequent) pregnancy because of the well-known fact that the first child usually escapes. However, a careful obstetric history should always include transfusions given the mother at any age; if blood has been given, testing for antibodies is indicated even in the first pregnancy. This should be done even if the transfused blood was reliably tested as Rh-negative because of the possibility of sensitization to factors other than Rh. It also should be done in Rh-positive mothers because of possible incompatibility in subfactors of the Rh (or CDE) complex. Whenever possible, the tests should be performed with the husband's erythrocytes as well as with standard group O Rh-positive and Rh-negative cells, so that any antigen in which the fetus might differ from the mother will be included. While these are technical problems for the blood bank expert, the responsibility of the physician is clear.

In attempting a prognosis for the infant when maternal antibodies have been demonstrated, I have found that the titer is less informative than the history. Sensitization of the mother by transfusion is especially to be feared. In general, stillbirths tend to repeat themselves. If a previous child was affected but live-born and nearly full term, chances for another viable infant are very good.

Space limitations preclude discussion of the indications for exchange transfusion. The danger, as the physiology of hemolytic disease is now understood, is chiefly twofold: The first is cardiac failure, which is usually self-evident and goes hand in hand with severe anemia, marked visceromegaly and normoblastemia. Here the indication is for venesection via the cord and for cautious partial replacement of withdrawn blood by packed erythrocytes. The second and more common danger is hyperbilirubinemia, for which exchange transfusion is the only effective treatment at present. Here, much depends on the rate of rise of the bilirubin level and the facilities at hand to follow the infant chemically and clinically. When in doubt, the qualified operator had best do an exchange. In specialized centers there will be less frequent need for this procedure. In any event it should be done slowly to allow equilibration between the bilirubin in the extravascular space and that to be removed from the blood.[7] Relatively large volumes are desirable if the infant tolerates the procedure well.

The choice of blood is no problem in typical cases with Rh-negative mother and Rh-positive infant. Group specific Rh-negative blood is to be preferred. Where this is not available, so-called low titer group O blood will do. The problem which arises from time to time is that of antibodies not of the usual specificity but anti-Hr (anti-c) and those not related to the Rh system. In such cases the donor blood which can be crossmatched by a sensitive method (Coombs' test) with the mother's serum should be chosen, but if this cannot be obtained it is better to use incompatible blood of the suitable major group than to let an infant die of cardiac failure or even of bilirubin encephalopathy. In an emergency, any group O blood is better than none.

ABO hemolytic disease is generally milder, in terms of hemolysis and anemia, than is Rh hemolytic disease. Its chief clinical sign is early jaundice, which often becomes quite marked. Its chief hematologic stigma is spherocytosis. The serologic diagnosis offers difficulties. The combination of mother O and infant A or B must be present but is not in itself diagnostic. Maternal antibodies are likewise of limited value in the ABO system. In my laboratory, the best correlation with the clinical diagnosis has been obtained with the following test: The serum of the infant is incubated with adult erythrocytes of the same blood group as the infant himself, A (i.e., A_1) or B, and with group O cells in a control test. The tubes are observed for agglutination and, if negative, the cells are washed and subjected to the Coombs test. The presence of an antibody affecting adult cells of the same blood group was observed in 97 per cent of ABO hemolytic disease.[8] The test is rapid and therefore useful.

In treating ABO hemolytic disease, the same general criteria used for Rh hemolytic disease should be followed. The physician should bear in mind that virtually the sole danger to infants with this disease is kernicterus, i.e., bilirubin encephalopathy.

Acquired auto-immune hemolytic anemia—This condition occurs at any age; the youngest patient we have had in our clinic was four months old at the time of diagnosis. It is by no means established whether the serum globulins reacting with the patient's (and usually all or many other human) erythrocytes are true antibodies in the sense of being the response to an immunologic stimulus. Conceivably, they are simply abnormal serum proteins produced by an abnormal liver and having the accidental property of reacting with erythrocytes. But the reactions are usually comparable to those of true antibodies—auto-agglutination, a positive direct Coombs test, often a positive indirect Coombs test with other erythrocytes, and other serologic findings admirably described by Dacie.[1]

The onset of this type of anemia in children is often abrupt, with severe anemia, pallor, jaundice, fever, abdominal pain, in some instances hemoglobinemia as evidence of rapid intravascular hemolysis, and the general clinical picture of an acute grave illness. Spleen and liver are enlarged, and liver function tests often show considerable abnormalities. The typical hematologic findings may be temporarily obscured by an erythroid aplasia of the marrow at the onset, or they may be accentuated by marked leukocytosis with "left shift." There are pronounced spherocytosis, increased osmotic fragility and, eventually, reticulocytosis of high degree.

The etiology of auto-immune hemolytic anemia is not uniform and is often obscure, especially in the pediatric age group. Collagen disorders, hepatitis, infectious mononucleosis, malignant lymphomas[9] and a host of other associated diseases have been reported.

The diagnosis rarely presents difficulties, but therapy does. Transfusions present a special problem in these patients, because they are often required on an emergency basis; yet the proper typing alone is difficult because of the tendency of the patient's erythrocytes to agglutinate in any serum or high protein medium. We have seen several Rh-negative patients who had been mislabeled at the referring source and had received Rh-positive blood. Because of the presence of antibody, crossmatching is usually impossible if the tests are done by a sensitive technic such as the Coombs test, as is proper. It is my opinion that any transfusion given to such a patient is a medi-

cal, i.e., blood bank, emergency which, if at all possible, should be undertaken only by experts in blood bank problems. Where such are not available, transfer of the patient to an appropriate center is preferable, provided there is sufficient time.

Empirically, steroids are usually effective in acquired hemolytic anemia. The dosage must be determined by trial and, if necessary, by error. It is best to begin with a large dose and, as soon as improvement has begun, to reduce the dosage cautiously, increasing it again in relapse. Oral cortisone, hydrocortisone or prednisone is usually satisfactory. In case of failure, some authors recommend a trial with ACTH. It is our practice to decrease the dosage and entirely wean the patient from steroid therapy if the trial shows that he can maintain his hemoglobin level. Therapy is started again when relapse occurs. Initial and intercurrent infections are treated strenuously with a suitable antibiotic, preferably one to which the patient has not been previously exposed.

The course of this disease is highly variable and unpredictable. In some instances, the Coombs test becomes negative after a relatively short time, and the patient may be permanently cured. Sometimes, years of chronic or intermittent hemolysis are observed. In some instances, the Coombs test remains positive for years but there is little or no hemolysis in the absence of further therapy. In such cases one should treat the patient, not the Coombs test!

Splenectomy is generally a last resort. Its results are quite unpredictable. It should be reserved for those patients who no longer respond to steroid hormones. This view furnishes an additional reason for tending toward a minimum dosage or complete curtailment of hormone therapy whenever possible. It is easier to return to such therapy when necessary than to maintain it for long periods.

Hemolytic anemia with naphthalene poisoning—Finally, a form of hemolytic anemia should be mentioned which, in this country, is relatively common in the age group from two to four years. This is the acute hemolytic anemia sometimes resulting from ingestion of naphthalene, usually in moth ball form.[10]

Recently, it has become clear that the susceptibility to naphthol derivatives is a genetically determined trait[11] that is found in some Negro children. Hence, in most children anemia does not develop after ingestion of naphthalene. Those in whom it does have a dramatic illness with lethargy, fever, diarrhea, jaundice, hemoglobinemia and hemoglobinuria; there also is some degree of hepatosplenomegaly. The blood picture is highly characteristic in that many erythrocytes show bizarre fraying, segregation of hemoglobin, lysis and tearing in addition to sphering. The blood film in typical cases is diagnostic. A history of ingestion of naphthalene can usually be obtained.

Treatment is entirely symptomatic and consists of blood transfusion as indicated, hydration, and prevention of intercurrent infections.

Comment

In the space allotted it has not been possible to discuss all the hemolytic anemias occurring in childhood or to give an adequate description of each of those considered. In this brief review, emphasis has been placed on characteristically pediatric conditions and on points which seem important in the newer understanding or management of these states.

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